THE Journal of the Kansas Medical Society

NOVEMBER
1961

VOL LXII
NO XI

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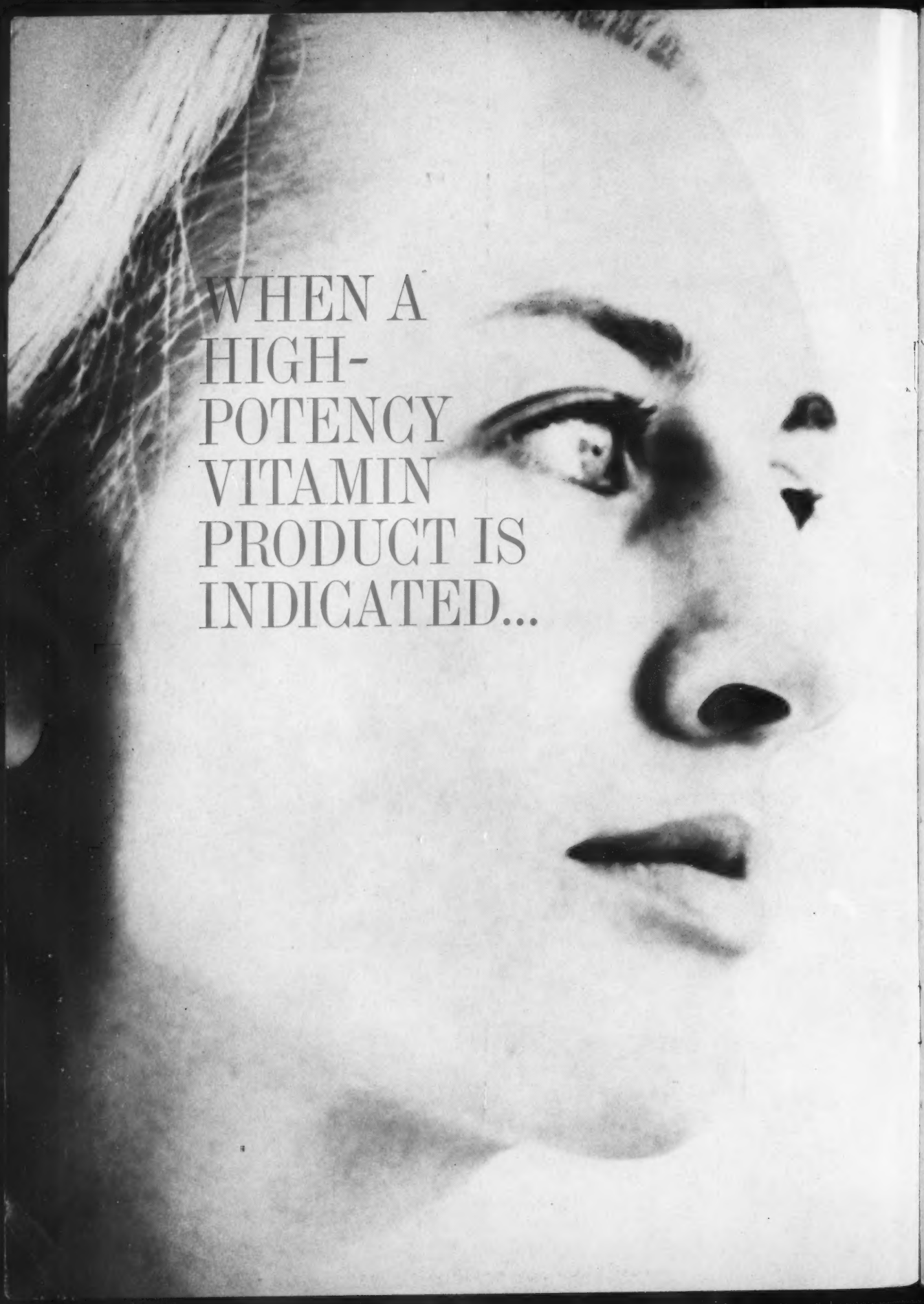
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Volume LXII, Number 11—November, 1961

The JOURNAL of the KANSAS MEDICAL SOCIETY

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Business Manager: Oliver E. Ebel, 315 West Fourth Street, Topeka.

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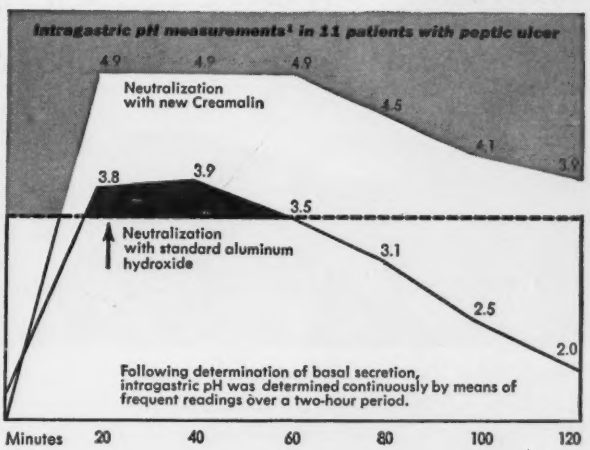

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Wednesday, November 1, 1961
The Colony Motor Hotel

HARRISBURG, PENNSYLVANIA
Thursday, November 9, 1961
The Penn Harris Hotel

JACKSONVILLE, FLORIDA
Sunday, November 12, 1961
The Robert Meyer Hotel

ALLENTOWN, PENNSYLVANIA
Wednesday, November 15, 1961
The Americus Hotel

SOMERVILLE, NEW JERSEY
Thursday, November 16, 1961
The Far Hills Inn

NASHVILLE, TENNESSEE
Wednesday, November 29, 1961
Meharry Medical College

EDINBURG, TEXAS
Saturday, December 2, 1961
The Echo Motor Hotel

WACO, TEXAS
Sunday, December 10, 1961
The Holiday Inn

Plans for 1962 already include the following Symposia, with more being arranged:

MOBILE, ALABAMA
Friday, January 5, 1962
The Admiral Semmes Hotel

ST. PAUL, MINNESOTA
January 8, 1962
The Hotel Lowry

PORTLAND, OREGON
Wednesday, January 24, 1962
The Sheraton-Portland Hotel

ANCHORAGE, ALASKA
Saturday, February 24, 1962
The Westward Hotel

WINCHESTER, VIRGINIA
Wednesday, March 14, 1962
The Lee-Jackson Hotel

SIOUX CITY, IOWA
Thursday, March 15, 1962
The Sheraton-Martin Hotel

SPOKANE, WASHINGTON
Saturday, June 2, 1962
The Davenport Hotel

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1. Clark, T. E., and Jochem, G. G.: Angiology 11:361 (Aug.) 1960.

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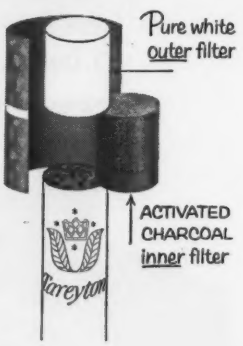

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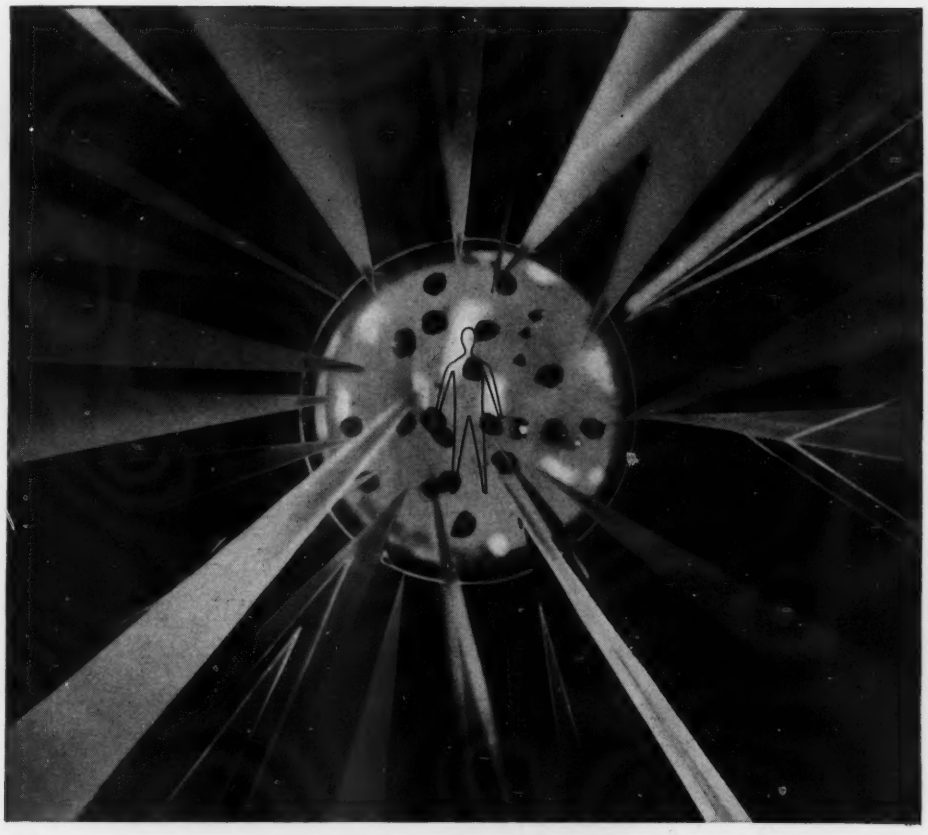

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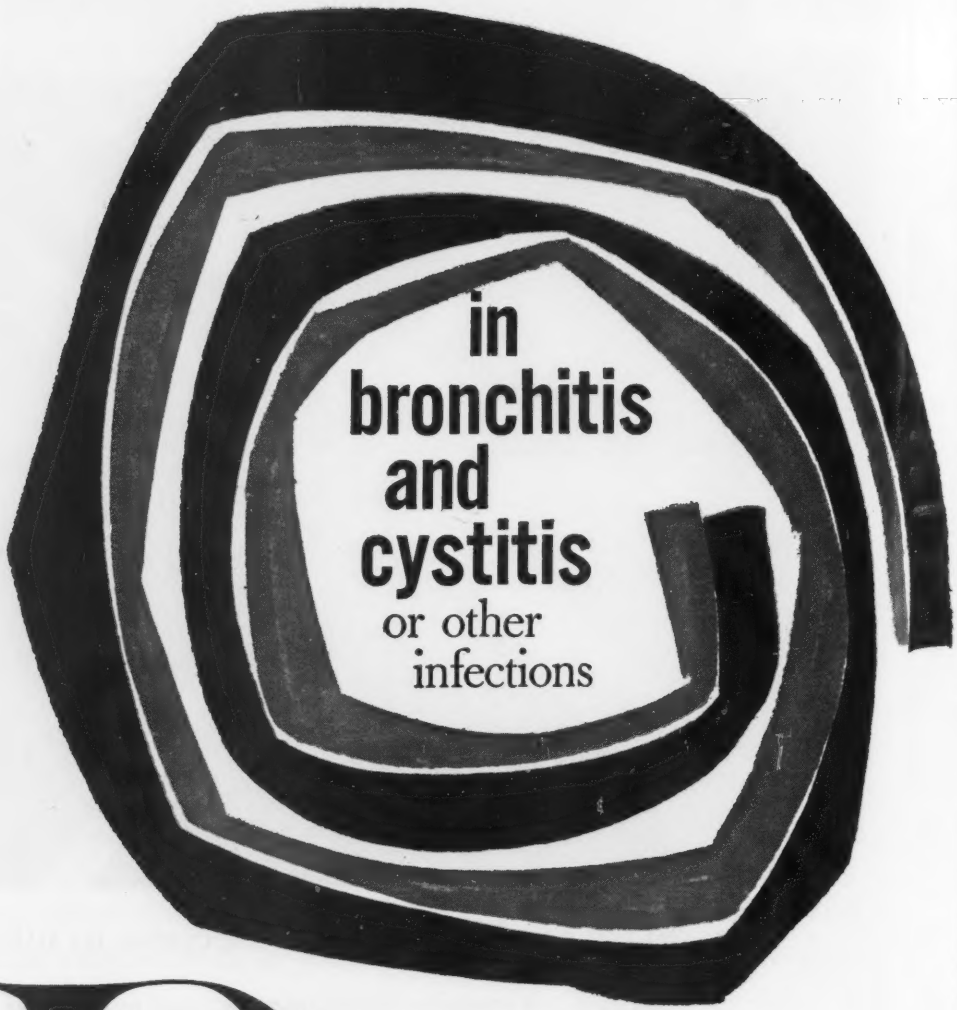

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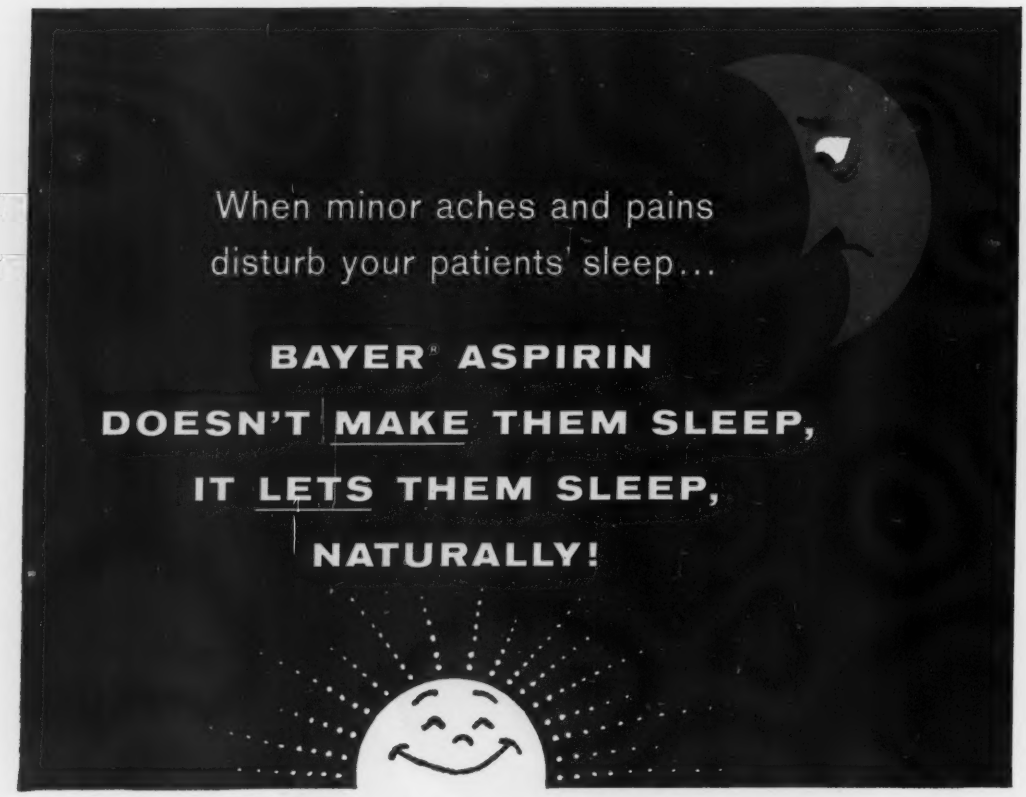

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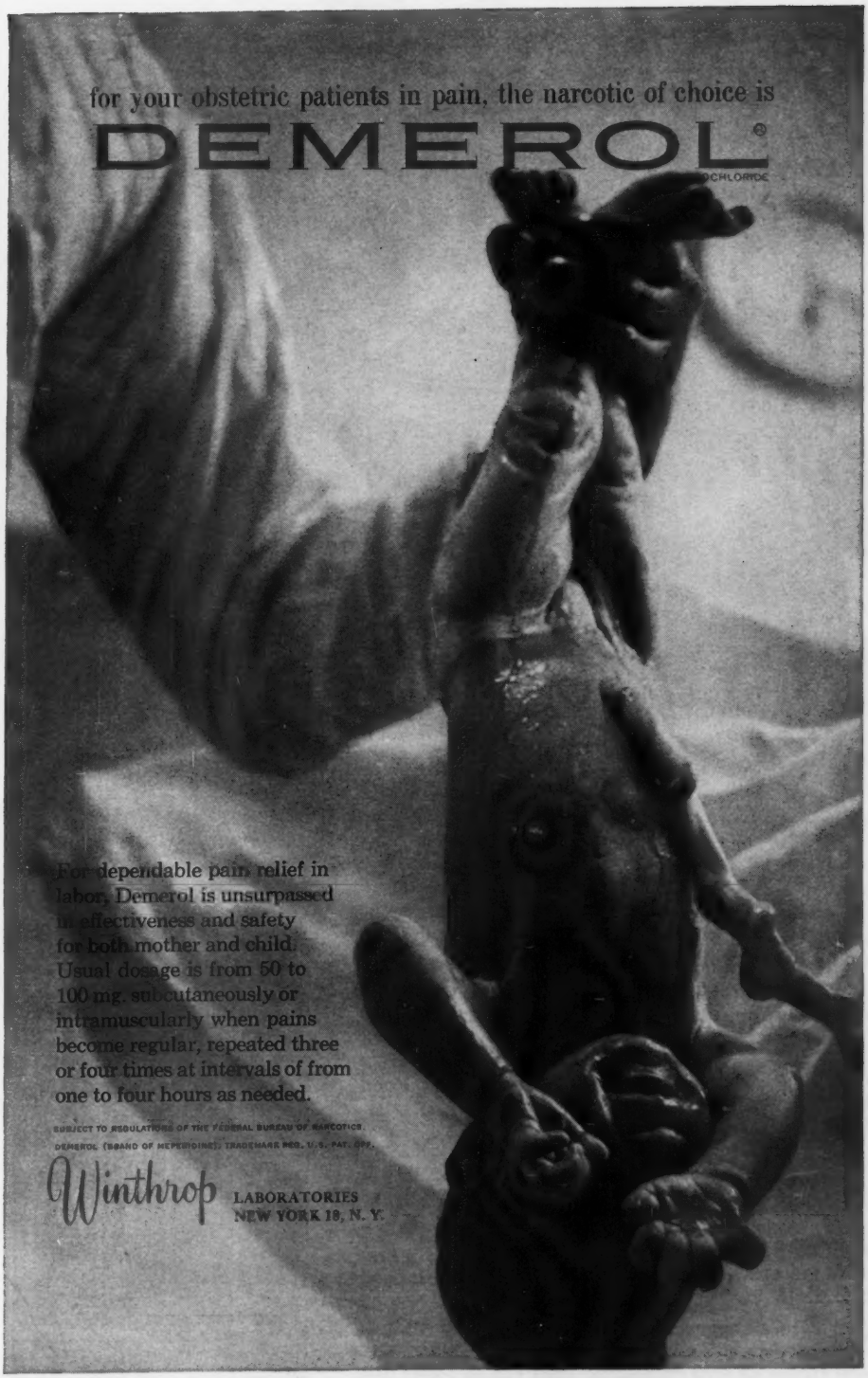
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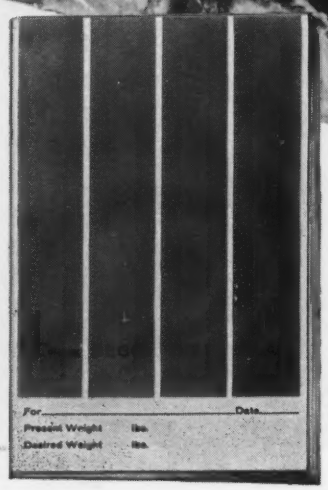

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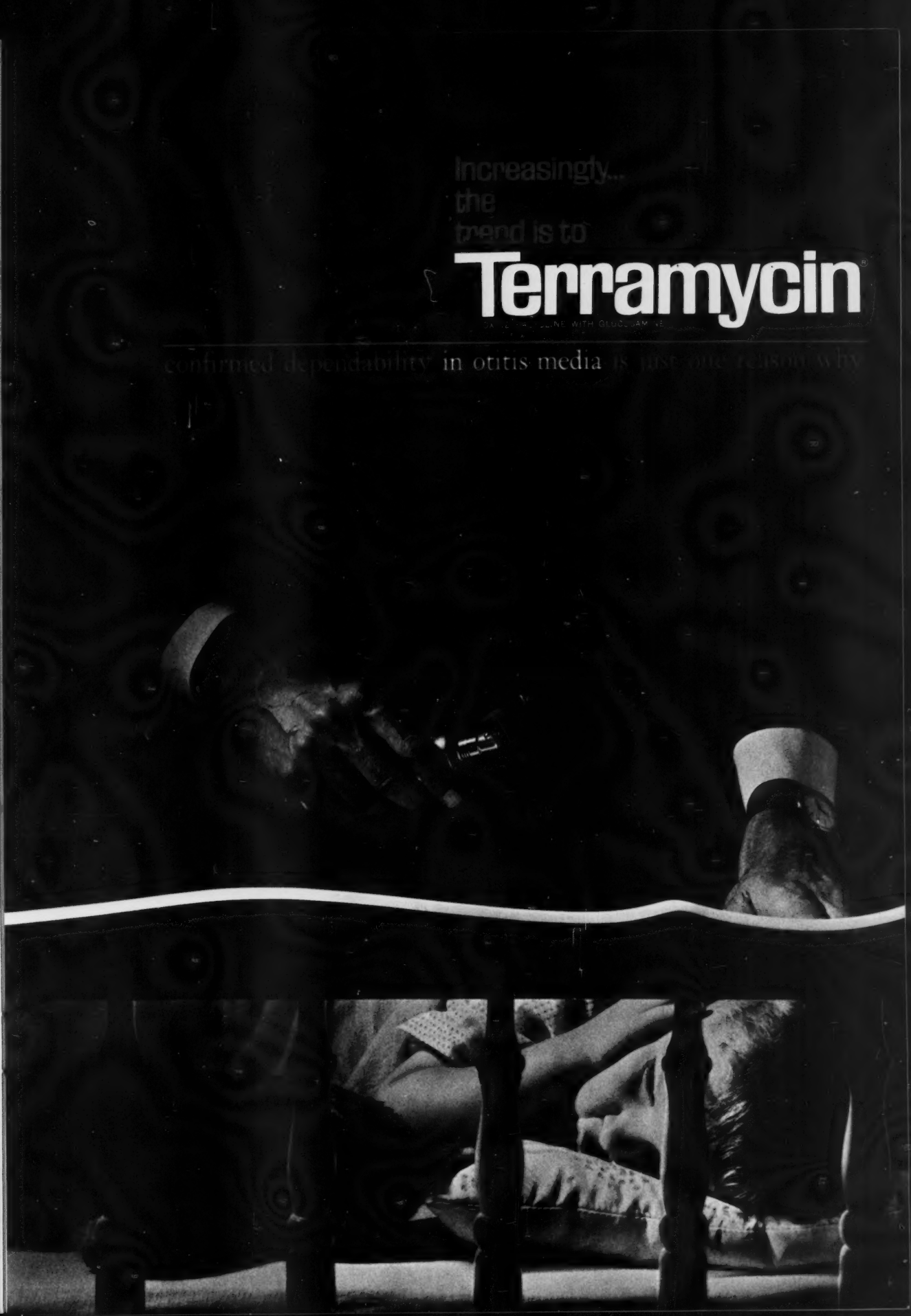

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*Jacques, A. A., and Fuchs, V. H.: J. Louisiana M. Soc. 113:200, May, 1961.

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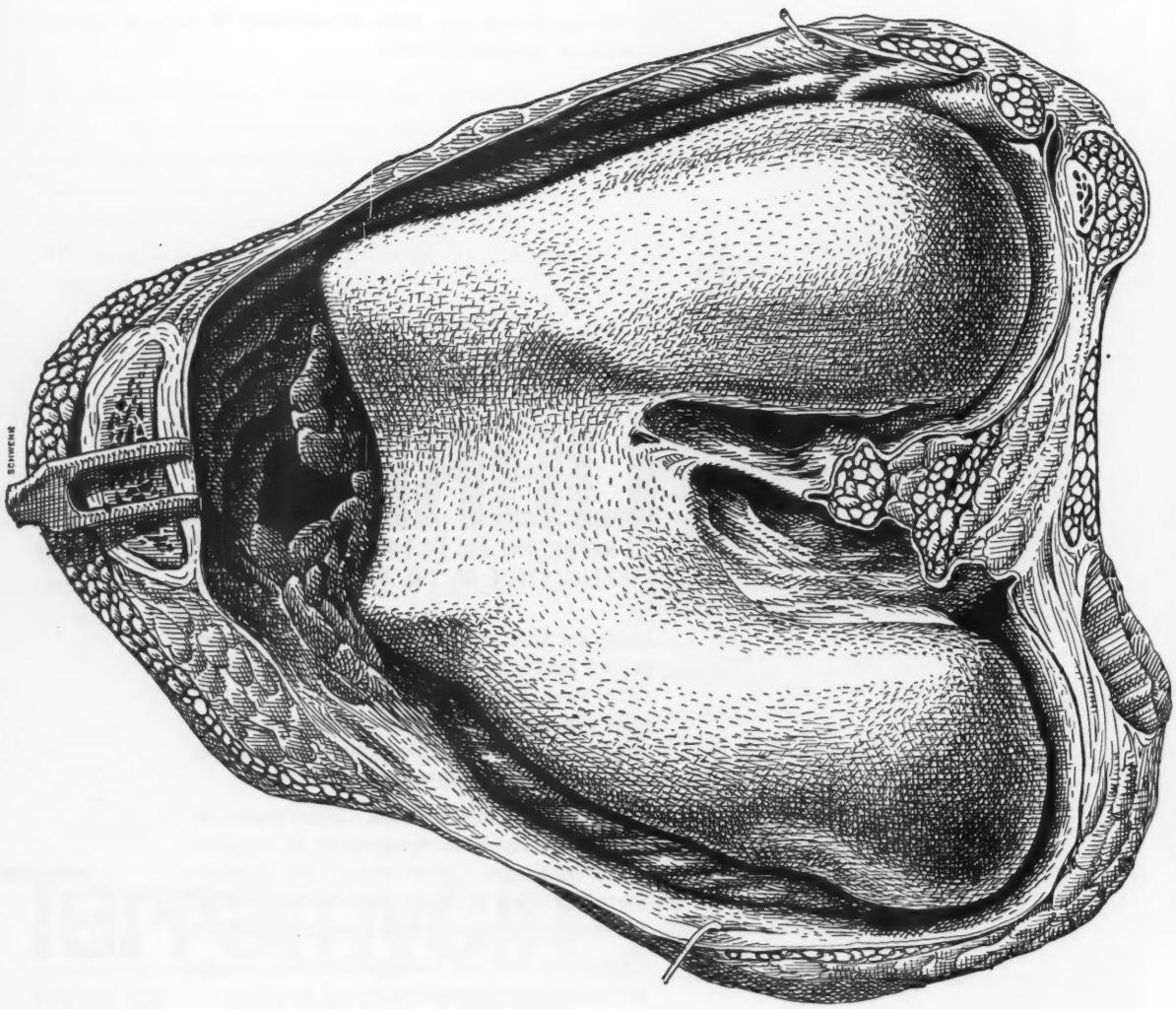

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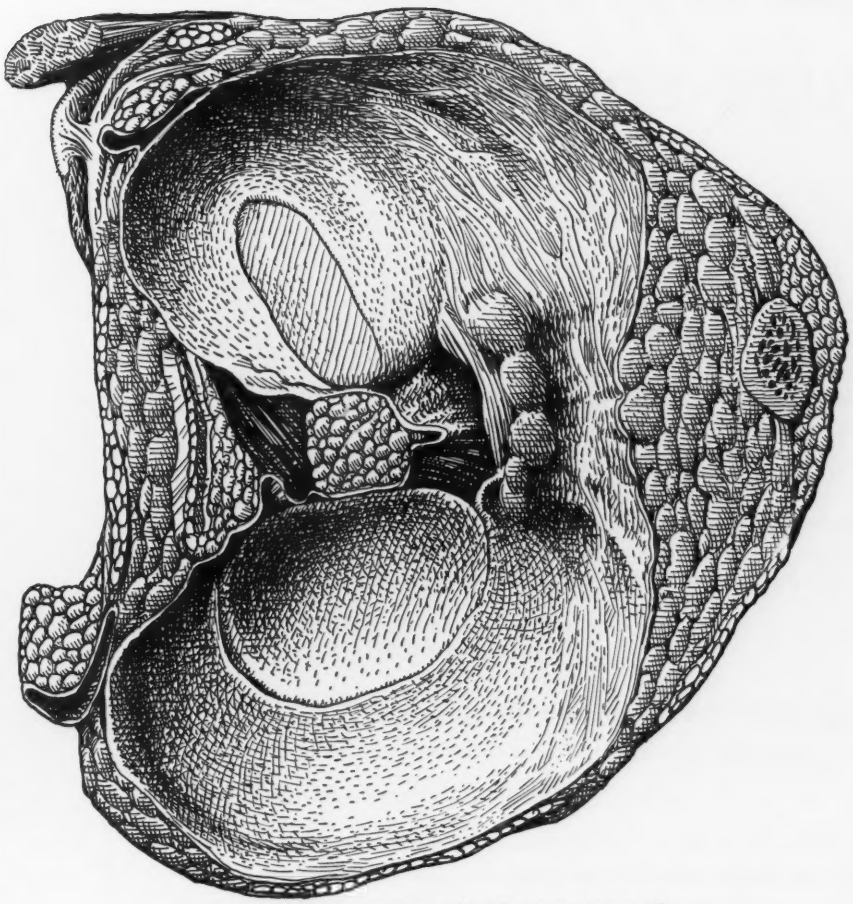

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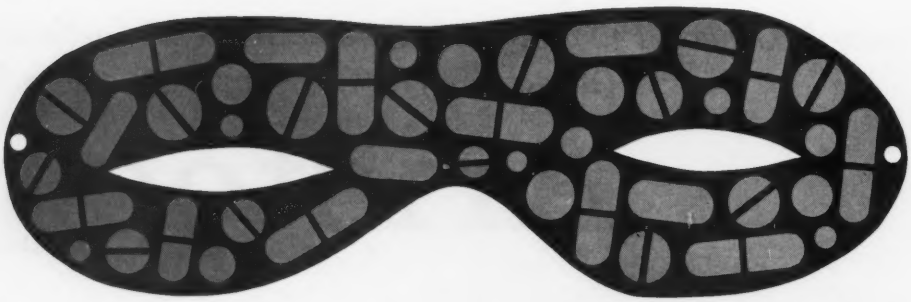

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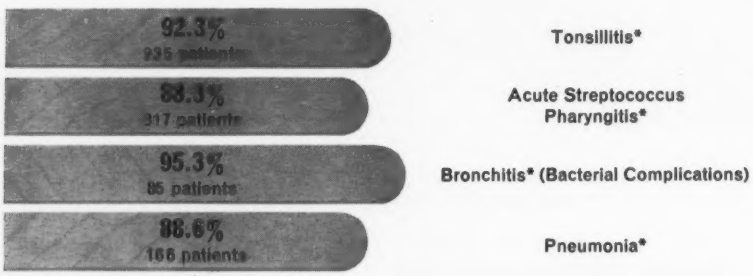

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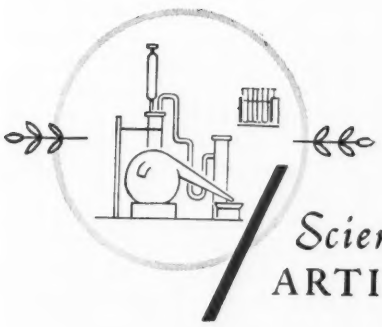

Scientific
ARTICLES

Detection of Cancer

The Interrelationship of Dentists and General Practitioners in the Detection of Cancer

I. PHILLIPS FROHMAN, M.D., ***Washington, D. C.***

WHEN WE SPEAK of the relationship of physicians and dentists in the detection of cancer, we must more or less restrict our discussion to the detection of cancer of the face, neck and oral cavity. Since it is not usual for our professional associates in the field of dentistry to do complete physical examinations, we physicians do not expect them to find cancer of the breast, lungs, stomach or cervix. Yet, is this too much to ask? What about the complaints registered by so many patients visiting their dentists for emergency or routine dental examinations and treatment? How many times has the dentist heard the remark, "Doctor, I have a bad breath. I think my gums or teeth are causing it." Or again, "Don't you think my teeth might cause my stomach pains, since I can't chew my food properly?" Or, "I have pains in my back (or arms or hand). Do you think some infection in my gums is causing this?"

I feel quite certain that my dentist colleagues have heard all sorts of complaints blamed by patients on their teeth, gums, or anything else in the oral cavity. Some of these complaints might very well be the only clue and the cue that this patient must be seen by his family doctor for a complete checkup. Many patients will take care of their teeth, for they are visible at all times, but will neglect the rest of their body. It is at the time when the dentist hears these complaints from his apparently healthy patient that he must suggest—no, insist—upon a complete physical examination by that patient's physician.

I firmly believe that if every dentist would take time during the first visit of a patient to listen for 15 or 20 minutes to his patient's complaints—not only those pertaining to the oral cavity, but general complaints—and allow the patient to talk about his entire physical being; and the dentist would insist that complaints other than those of the oral cavity must be investigated by a physician, I venture to guess that we physicians would detect more early cancers of the stomach, intestinal tract, lungs, breasts, uterus, and other areas than we do now.

The critical position of the dentist in cancer control and his relationship with the family physician are important in two ways. First, most of the American public have been educated to the fact that they should visit their dentist at least once a year, and thus the dentist has a better opportunity to see and examine the apparently healthy population. Second, the observant dentist will, in most instances, see patients with symptoms of oral cancer before these patients are seen by their physicians. Since the patient having oral cancer usually attributes the early lesion to faulty teeth or dentures, he commonly visits

Presented at 1961 Midwest Cancer Conference, Wichita, Kansas, March 17 and 18, 1961.

the dentist first. If the dentist is circumscribed in his knowledge, with a focal point of his vision, his training and his interest upon teeth alone, many cases of precancerous or cancerous lesions in the early stage will be missed completely.

Likewise, physicians may feel that there is no reason to examine thoroughly the oral cavity and, unless the patient complains of oral lesions or dental difficulties, these physicians will also miss early or late lesions. The obstetrician who is mentally intent upon delivering babies or healing a cervical erosion or performing a hysterectomy, may, in all probability, not be disturbed about the other end of his female patient: the oral cavity. The orthopedist nailing a fractured hip or reducing a fracture of the wrist may also forget that his patient has an oral cavity full of potential cancer sites. These and other physicians, in many instances, have no occasion to examine the oral cavity, and therefore early lesions and frank cancer masses may go unnoticed until spread beyond help or hope.

These reasons are no excuse for the internist, the general physician, or the dentist. All of us must seek out these lesions rather than wait for symptoms and patient complaints.

Both the dentist and the physician face a grave responsibility and obligation for thorough examination, diagnosis, treatment and care of the oral cavity. The primary duty of both professions is proper, early and accurate diagnosis. The dentist has the advantage in that he sees many thousands of patients who, since they are apparently in excellent health, rarely visit the physician. Most of them say, "Nothing bothers me. Why should I see a doctor?" Our colleagues in the dental profession are about a quarter of a century ahead of the medical profession in that they have educated their patients for many years to visit their dentist every six months or so for routine prophylactic dental care. It is regrettable that we physicians have not been as successful in our plea for regular, periodic, preventive examinations.

Five per cent of all human cancers are those of the oral cavity. Excessive exposure to wind, frost and sunshine is by far the most frequent predisposing factor in producing carcinoma of the lower lip. Cancer of the buccal mucosa is more frequent among smokers and habitual tobacco chewers than among the population in general. Poor oral hygiene, improper diet (not necessarily malnutrition), trauma and other forms of localized irritation are important etiologic factors which can be elicited from good histories taken by the dentist and the physician. Repeated trauma due to biting or malfitting dentures will produce hypertrophy of the mucous membrane and must be differentiated from true tumors. Just as important, the cause must be corrected or eliminated.

Cancers of the oral cavity, face and neck are accessible to sight and touch and should be detected early if proper examination is made. Both physicians and dentists must forever keep in mind the causative factors in producing cancer of these areas. The dentist, as well as the doctor, should and must know how to examine the neck for palpable masses in the thyroid gland and enlarged cervical lymph nodes.

All patients visiting dentists, whether for routine dental and oral checkup, or for emergency care, should have a complete blood count done! It has been stated that the high incidence of cancer of the oral cavity, pharynx and esophagus in Swedish women is due to iron deficiency, Plummer-Vinson syndrome—anemia, achlorhydria and atrophy of the mucous membranes of the mouth and pharynx. This is a true precancerous condition.[1]

I would also suggest that a complete urinalysis on all dental patients would help greatly to uncover acute or chronic conditions of the urinary tract and diabetes. And a serology on all adult dental patients, as a part of the dental examination, would be truly preventive medicine.

Leukoplakia, papilloma fissure and ulceration about the mouth are precancerous lesions. These lesions in inherently susceptible individuals have a tendency to undergo malignant change when subjected to sufficient irritation over a long period of time. Syphilitic leukoplakia usually becomes cancer, and syphilitic warts, fissures, gumma and atrophic glossitis may also precede cancer.

Transformation of polyps of the tongue into carcinoma has been observed. Leukoplakia is a chronic, painless inflammation commonly seen, and more commonly overlooked or disregarded, in the oral cavity and larynx and may be found on the dorsum of the tongue, lip, gingiva, buccal mucosa and palate. Etiologic and predisposing factors include atrophic glossitis, vitamin A deficiency, alcohol, tobacco, syphilis, and irritation from dental appliances such as crowns and bridges. Many cases of leukoplakia can be corrected or eradicated by elimination of the cause, and it is for this reason that the physician must be as well educated and as highly interested as the dentist in cause and effect of lesions in and about the oral cavity.

Failure to recognize the existence of an abnormality could cost the patient much destructive surgery or even his life. When a lesion is seen or felt, it is mandatory that something be done about it. Procrastination—to "wait and see what develops"—may be a sentence to facial deformity or widespread cancer metastases and loss of life. The urgency for early examination and immediate remedial steps for any lesion about the face and oral cavity can best be brought home by these statistical figures:

Oral cancers include those of the lips, buccal

mucosa, gums, palate, tonsils, floor of the mouth and tongue. The five-year cure rate of all cases of the oral cavity as compiled by the American Cancer Society in 1958 are shown below in Figure 1.

The systematic exploration of the oral cavity and face for signs of infection or disease, lumps and nodules, indurations and leukoplakia, is often neglected during the physical examination. The physician who will not hesitate to do rectal examinations with a sightless finger upon most or all of his patients more often than not may skip the examination of the oral cavity with both eyes and fingertips. Examination will reveal so much with so little effort and time. The use of adequate lighting, a tongue blade or other depressor, a dental mirror, gauze, plastic or rubber gloves or finger cots are the only equipment necessary.

Begin with the face, lips, jaws, parotid glands, and the submandibular and submental areas. From this point the intraoral structures should be visualized and palpated beginning with the anterior structures and then the posterior oral structures and pharynx. A good routine procedure, always in the same order, should be: lips, cheeks, floor of the mouth, tongue, palate, tonsillar area, posterior pharynx, retromolar area and gingiva. After careful inspection, these same areas should be thoroughly palpated with the gloved hand to find any areas of swelling, roughness, discoloration, induration, asymmetry, or change in function of the tongue. A tongue blade and dental mirror are helpful for the examination of the dorsum of the tongue after the tongue is covered with gauze and pulled forward to expose the lateral borders, as you simultaneously push the cheek laterally with the tongue blade. The dental mirror will expose the base of the tongue and pharynx.

Palpation is significantly important, both by the dentist and by the physician. By adequate palpation we can feel whether a swelling on the lip or cheek is indurated or firm, whether cystic or nodular. It is not enough for the physician to depress the tongue and ask the patient to say "ah." It is important to examine thoroughly the tongue, especially the base of the tongue, to see and feel any asymmetry or abnormal amount of lymphoid tissue on either side.

Physicians and dentists must be acquainted with

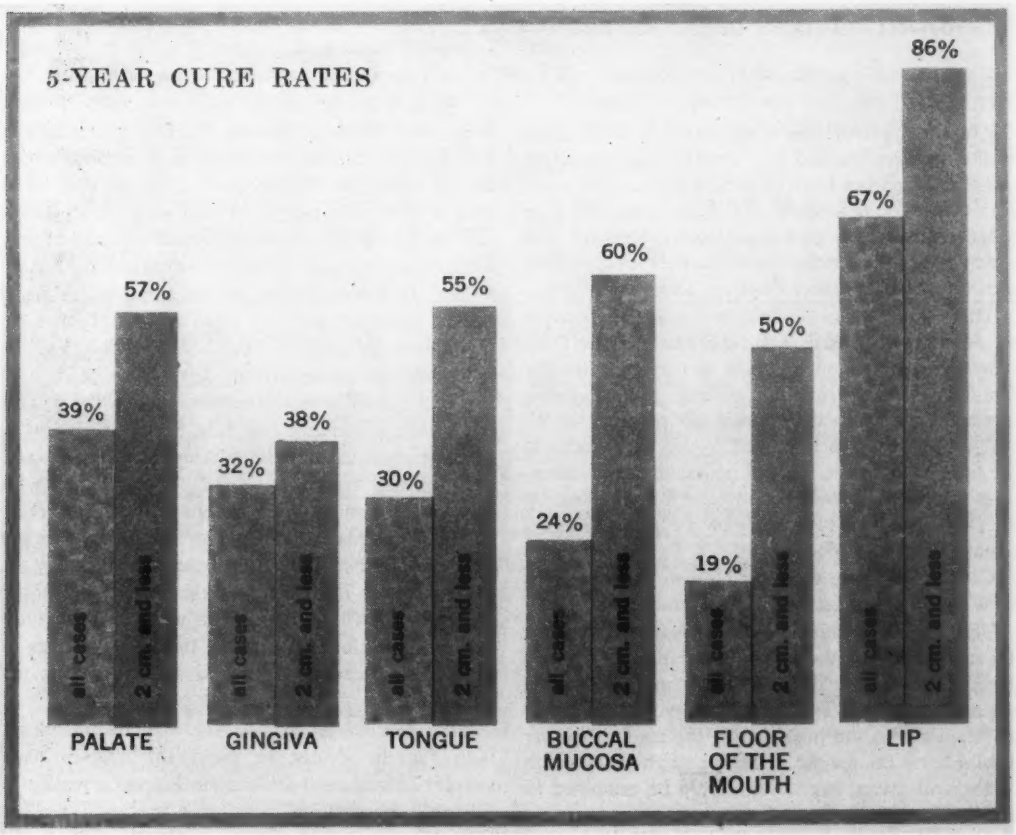

Figure 1

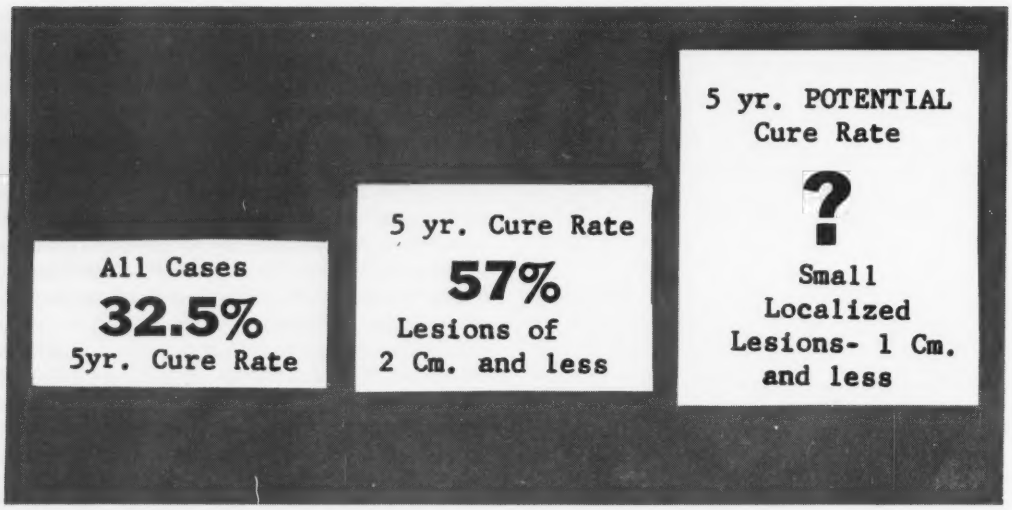

Figure 2

the various types of lesions encountered on the face, in the neck region, and in the oral cavity, including the lips. Much has been written, with excellent color plates, in various medical and dental journals. It is not the purpose of this paper to try to cover that which has been written so adequately by excellent men interested in cancer detection and eradication.

There is no excuse for either dentist or physician to miss any of these oral-facial lesions. Lack of thorough examination by either is negligence in the first degree. As with cancer elsewhere, early diagnosis is vital. Sage states that "about 40 per cent of all oral cancers have metastasized to the neck nodes at the time of diagnosis." This high incidence of metastases is more than likely due to patient procrastination and, secondly, lack of urgency on the part of the examining dentist or doctor.

Cancer, like time, waits for no man to prepare for it. We must see it, feel it, biopsy it and excise it.

The first step in obtaining necessary knowledge about the patient is the history in detail, including his present complaint or illness (if any) and past medical and dental history. The dental history should be just as important to the physician as the medical history should be to the dentist. After thorough examination of the oral cavity, any lesion should be examined in detail to attempt to determine its nature and cause. At times it may be necessary to do hematologic, bacteriologic and histologic studies. The biopsy specimen is the most valuable and most used method to determine the nature of the disease process and its etiology. I believe that both physicians and dentists are much too timid in doing biopsies on small lesions, lest they subject their patients to needless excisions on benign lesions. Is it harmful to remove a normal or near-normal appendix when the signs and symptoms seem to indicate an acute appendicitis? Certainly not! Is it harmful to excise a small, suspect lesion, one to two centimeters in diameter, even though the pathologist finds it benign? Certainly not! The patient is much relieved to know he does not have cancer, and the physician or dentist should be most happy with the news. In many years of practice, I have yet to have one complaint from any patient when a biopsy report is returned from the laboratory as negative. A good example is the many thousands of diagnostic uterine D and C's done each year without the slightest patient complaint. Let's not be timid. Let's excise to be certain. Let's not "wait and see" until it is too late.

The decision to biopsy for definite diagnosis, both for the dentist or physician, resolves itself simply: If it doesn't look right, biopsy or excise it. "Periodic observation" or "let's wait and see" is dangerous in most instances. Procrastination on the

part of the patient is unfortunate; on the part of the doctor or dentist it is unforgivable.

Any ulcer which persists for two or three weeks without evidence of healing, persistent hyperkeratotic changes in surface tissue, palpable or visible mass on or beneath the normal surface tissue, any inflammatory changes which persist for prolonged periods, and any bone lesions not readily identified by x-ray or clinical observation—all of these and others—must be biopsied or completely excised. If you, as physicians or dentists, do not do these procedures, please refer patients needing such care to a colleague who does—and refer the patients NOW!

The control of cancer continues to be of great concern to all of us. Over one-quarter of a million deaths will occur in 1961 from cancer. Some of these deaths can be avoided. Oral cancer can and should be diagnosed early and removed immediately, thus eliminating it from the list of body areas producing death due to cancer. In some sections of this country, cancers of the head and neck represent ten per cent of the total cancer deaths. This is inexcusable. We must forever be observant of any deviation from normal in the skin of the face and contour of the neck, and even the slightest deviation from normal in the oral cavity. Not only must we be cognizant of these differences, but we must do something about them immediately.

The family dentist, well trained and educated in the problems of cancer detection and treatment, holds a unique place in the community for cancer detection, since approximately 50 per cent of his patients come to him without having seen a doctor for a physical examination. If the physician does not see the patient, he cannot detect cancer.

The basic interrelationship between dentists and physicians is one of mutual understanding of the goal in the detection and eradication of cancer of the neck, face and oral cavity. It is, I firmly believe, most important that the dentist procure a thorough history from his patients, not only referable to the oral cavity, but a general history of the patient's complaints of all body systems, from belching to flatus. He should note if the patient has chest pains, headaches, shortness of breath, changes in bowel habits, chronic cough, night sweats and weight loss. In other words, our colleagues should obtain a good medical history before engaging themselves too deeply in the oral cavity. By getting this type of history, more than likely a large portion of the fifty per cent of the dental patients who have not visited a doctor would be referred for medical examination and diagnosis. In this manner, a great many of the late cancers seen by us would be early cancers that could be helped, with thanks to our dental colleagues.

Likewise, the physician should and must do more than a simple, cursory examination of the oral cavity. He must refer to the dentist any and all patients who show the slightest deviation from normal in the oral cavity, whether it be teeth, dentures, ulcerations or masses.

Working together, physicians and dentists can give our patients the finest care and can produce early eradication of cancer potentials and early cancers.

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2. Sage, H. H.: Oral and Facial Cancer, New York J. Med. 59:1113-1116 (March 15, 1959).

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4. Doe, J. E., What I Know About It, J. Kans. M. S. 54:717-719 (Dec.) 1954.

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Society members throughout the state are encouraged to write up their interesting cases and submit them for publication. The editorial staff welcomes the opportunity of helping you prepare your article for the printer.

Hemodialysis

Experience in Acute Renal Failure Treated With the Artificial Kidney

W. H. TU, M.D.,* ***Kansas City***

Thirty-four hemodialyses on 20 patients with acute anuria or severe oliguria were performed during the last 2 year period with the twin coil artificial kidney. There were 4 patients with primary extrarenal diseases presenting as acute anuria. A large portion of the patients were dialyzed because of potassium intoxication.

Usefulness of cation exchange resin in prophylaxis of hyperpotassemia, occasional incidence of hemostatic defect due to vitamin K deficiency and experience with arterio-venous teflon cannulae have been described.

HEMODIALYSIS is a unique means for the removal of metabolic end products, exchange of electrolytes and water in the treatment of renal failure. The purpose of this communication is to describe the clinical experience with the twin coil artificial kidney[1] at the University of Kansas Medical Center during the last 2 year period from January 1959 to December 1960 and to compare these with the results obtained during the preceding 2 year period from January 1957 to December 1958. Earlier experience with the clinical application of the artificial kidney has been described previously in The JOURNAL.[2]

Results

A total of 34 hemodialyses was performed on 20 patients with acute anuria or severe oliguria *(Tables I and II)*. This represents an increase in the number of patients and dialyses compared to the previous series when 11 dialyses were performed on 8 patients.

As with the previous series, potassium intoxication with advanced cardiotoxicity continues to be the major reason for hemodialysis. This was true in a total of 17 dialyses, 10 of which were done as an emergency. All the patients at the time of dialysis (except C. M. in Table II) had advanced uremia. Three of 10 patients who required emergency dialysis had anuria which was not due to primary renal disease *(Table II)*.

The over all mortality rate of 20 patients is 56 per cent; 44 per cent in 16 patients with acute tubular necrosis, with the highest in the postoperative patients (4 of 5) and 1 survival in 4 patients whose acute anuria was not due to primary renal disease. Four of 7 deaths in patients with acute tubular necrosis were complicated by severe staphylococcal septicemia at the time of the dialysis. Duration of oliguria or anuria does not appear to be directly related to prognosis. The number of patients in this series is small but the over all mortality rate agrees with the results by others.[3-7] Recently better results in a limited number of patients have been reported by maintaining patients relatively free of uremia by dialyzing them prophylactically daily.[4]

Cation exchange resin is effective in removing potassium through the gastrointestinal tract.[8] The merit of resin in treatment of renal failure is in prophylaxis of hyperpotassemia and it should be started early before the serum potassium concentration reaches a high level and while the clinical conditions remain well. Hemodialysis remains as the treatment of choice for potassium intoxication. In 3 selected patients orally given resin* was effective in preventing hyperpotassemia during the ensuing oliguria when it was started immediately after the hemodialysis. At this time the patients were clinically improved and able to cooperate but were still severely oliguric. Resin, mixed in 20 per cent mannitol solution, was given in small divided doses of 4 to 20 Gm. totalling 40 to 80 Gm. a day.

Semipermanent cannulation of radial artery and an adjoining arm vein with a pair of teflon cannulae[9] was used in 3 patients with good results. While patients are not on the artificial kidney this pair of cannulae is maintained open via an arteriovenous shunt without requiring heparin. Two patients remained severely oliguric for 30 days requiring 5 and 6 hemodialyses. The cannulae were placed in the arm the night before the dialysis and hemostasis was complete by the following morning. On 2 occasions the cannulae were thrombosed by the morning following cannulation. These cannulae, however, were flushed with saline-heparin solution and there was no recur-

From the Department of Medicine, University of Kansas Medical Center. This work was partly supported by the Greater Kansas City Chapter of the National Kidney Disease Foundation.

* Present address: Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

* Na-cycle carboxylic resin was kindly supplied by Dr. William Martz, Lilly Laboratory for Clinical Research, Marion County General Hospital, Indianapolis, Indiana.

TABLE I

PATIENTS WITH ACUTE TUBULAR NECROSIS

No.	Case	Age	Sex	Causes	Complications	K Intoxication	Outcome	Days Till Diuresis†	No. of Dialysis
1.	L. H.	59	M	T.U.R., Intravascular hemolysis	Pulmonary edema	+	R	10+	1
2.	B. H.	16	M	Automobile accident	Staphylo. septicemia, lung abscesses	+	D	9	2
3.	M. O.	16	M	Automobile accident	Renal colic, cong. hydronephrosis	+	R	6	1
4.	C. H.	58	M	Automobile accident		+	R	7	1
5.	C. M.	53	M	Ruptured aneurysm of abdominal aorta, embolism to leg	Hemorrhage of upper G.I. tract	+	D	30	5
6.	J. W.	27	F	Hemorrhagic shock at surgery	Staph. septicemia	+	D	12	1
7.	J. E.	58	F	Hemorrhagic shock at nephrectomy for cancer	Metastasis to liver		D	30	1
8.	A. B.*	40	M	Postoperative shock	Fever, dehiscence	+	R	30	6
9.	M. B.	31	M	Abdominal surgery	Staph. septicemia	+	D	23	5
10.	V. F.	26	F	Postpartum			R	12	1
11.	A. I.*	19	F	Postpartum	Uterine hemorrhage		R	29	1
12.	M. S.	62	F	Nephrotoxin (?)			R	16	1
13.	J. M.	30	M	(Alcohol intake)		+	R	4	1
14.	S. W.	19	M	Upper resp. inf., fever		+	R	8	1
15.	E. E.	46	M	Weil's disease		+	D	4	1
16.	C. O.	50	M	Electric burn	Staph. septicemia	+	D	20	1

* Prolonged prothrombin time which was corrected by vitamin K.
D: died
R: recovered
† Diuresis: 24 hour urinary output more than 1500 ml.

rence of clotting for the following month and blood flow of 300 ml. per minute could be maintained through these cannulae by a Sigmamotor without difficulty.

Illustrative Case: A 40 year old man went into a severe shock after an elective transabdominal vena cava ligation because of recurrent episodes of pulmonary embolism. His clinical course was complicated by dehiscence of the abdominal incision 5 days later requiring emergency surgery, stupor, repeated episodes of convulsive seizure and fever *(Figure 1)*. Since, after 2 hemodialyses it became obvious that he would require more, teflon cannulae were placed in his forearm. Thereafter, he was placed on the artificial kidney twice a week electively for 2 weeks with steady improvement. He made an uneventful recovery after 30 days of anuria, oliguria and 6 hemodialyses.

It is generally held that prothrombin content of plasma in acute uremia may be decreased but not to an extent to account for the hemorrhagic diathesis of uremia.[10, 11] Two patients, however, had hypoprothrombinemia to 20 per cent of normal and manifested unusually prolonged clotting time following the usual dosage of heparin or poor hemostasis to venipuncture and uterine bleeding. These defects were promptly corrected by administration of vitamin K with rise of prothrombin level. Thus vitamin K deficiency, either probably due to inadequate oral intake or possibly due to altered intestinal bacterial flora, should be ruled out before hemorrhagic defect is attributed to uremia.

Extensive areas of tissue necrosis should be debrided surgically since repeated hemodialysis may not be adequate to prevent a rise of serum potassium derived from the damaged tissue.

Illustrative Cases: A 16 year old boy (Case 2, B. H.) became anuric after spending a night with his leg pinned under an overturned automobile. He was placed on the artificial kidney twice at 24 hour in-

TABLE II

PATIENTS WITH ACUTE ANURIA (OR SEVERE OLIGURIA**) DUE TO MISCELLANEOUS DISEASES

Patient	*Age*	*Sex*	*Presenting Symptoms and Signs*	*Cause*	*History Indicative of Underlying Disease*
C. M.	44	F	Advanced potassium cardiotoxicity, shock, anuria	Exogenous supplementary K for low serum K	Potassium intake
M. H.	74	F	Advanced potassium intoxication, coma, hypotension	Multiple myeloma	Anemia, pathological fracture, arthritis
M. M.*	52	F	Anuria, hypotension, hypokalemia	K depletion nephropathy	Habitual laxative intake and enema food sadism
F. S.	59	M	Advanced potassium intoxication, anuria, coma, shock	Bilateral renal stones	Nephrolithiasis
E. H.	64	M	Potassium intoxication, anuria, pneumonia	Periarteritis nodosa	None

Case E. H. described previously, reference 2.
* Described in detail elsewhere, reference 12.
** Severe oliguria; 24 hour urinary output of less than 100 ml.

tervals, but his serum potassium level rose promptly to predialysis level of 8 mEq./L. soon after each dialysis. He finally died of staphylococcal septicemia and cardiac arrest. In 1960, another 16 year old boy (Case 3, M. O.), suffered from an identical automobile accident and injury to his leg. This time the crushed leg was amputated as soon as it was found that the rise of serum potassium and blood urea nitrogen was rapid. Ten hours after the amputation hemodialysis was performed with the conventional systemic heparinization technique. The dialysis was followed immediately by oral cation exchange resin be-

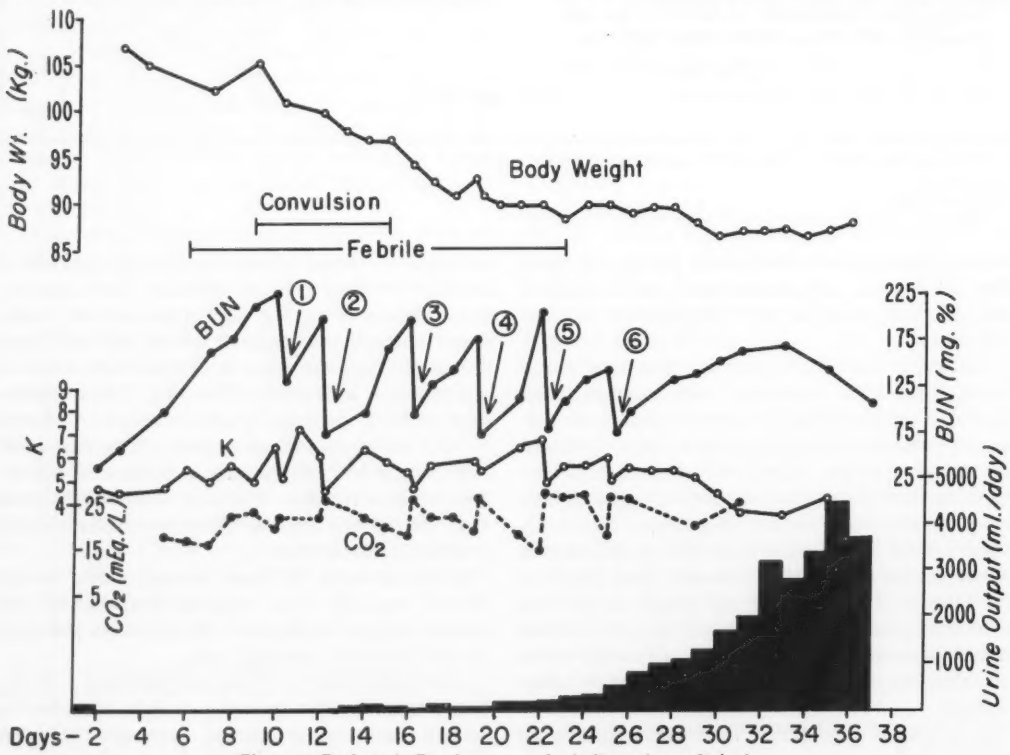

Figure 1. Patient A. B.: Arrow marks indicate hemodialysis.

cause his sensorium became clear and the nausea and vomiting disappeared. Serum potassium was maintained normal until diuresis started 3 days later. While he was passing copious amounts of urine during the diuretic phase he had several attacks of renal colic due to congenital hydronephrosis of the left kidney which had never been recognized. This was nephrectomized and he left the hospital in good condition.

In 2 patients, cases 13 and 14 *(Table I)*, the cause of acute tubular necrosis could not be adequately defined. Case 13, J. M. gave a history of heavy alcohol intake followed by nausea, vomiting and oliguria. He recovered quickly. Another patient, case 14, S. W. was interesting in that the disease might have been passed as an acute glomerulonephritis if tissue diagnosis of acute tubular necrosis by needle biopsy of the kidney had not been available. He was a 19 year old boy who was in good health until he developed fever, sore throat, generalized muscle ache and weakness and nose bleed. About 11 days later he was uremic (BUN 132 mg. per cent, serum K 8.0 mEq/L.) *(Figure 2)* and hypertensive (BP 154/110). Urinalysis revealed albuminuria, red cells, white cells and granular casts. At this time he was critically ill and complaining of pain, tenderness and weakness of muscles. He was placed on the artificial kidney with clinical improvement. Several hours later needle biopsy of kidney was performed without incidence. His urinary output was never less than 800 ml. per 24 hours throughout his illness and the diuretic phase was characterized by copious urinary output exceeding 6,000 ml. per 24 hours. Biopsy of muscle (gastrocnemius) and repeated measurement of urinary excretion of mercury were normal. He made an uneventful recovery.

Four patients in the current series and one in the previous series[2] had acute anuria and potassium intoxication (except M. M.*) as the presenting symptoms and signs of their diseases. Pertinent data of these patients are depicted in the Table II. The basic diseases are: potassium intoxication, multiple myeloma, bilateral renal calculi (died of potassium intoxication before he could be dialyzed), periarteritis nodosa, nephropathy of potassium depletion. These cases suggest that eiology of acute anuria should be searched diligently when the usual etiology for acute tubular necrosis can not be found. As Table II indicates, diagnosis may not be difficult if careful inquiry into the history is made for possibility of diseases which may be associated with involvement of the kidneys.

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* Described in detail elsewhere, reference 12.

The support and encouragement of Dr. Robert E. Bolinger, Associate Professor of Medicine is gratefully acknowledged.

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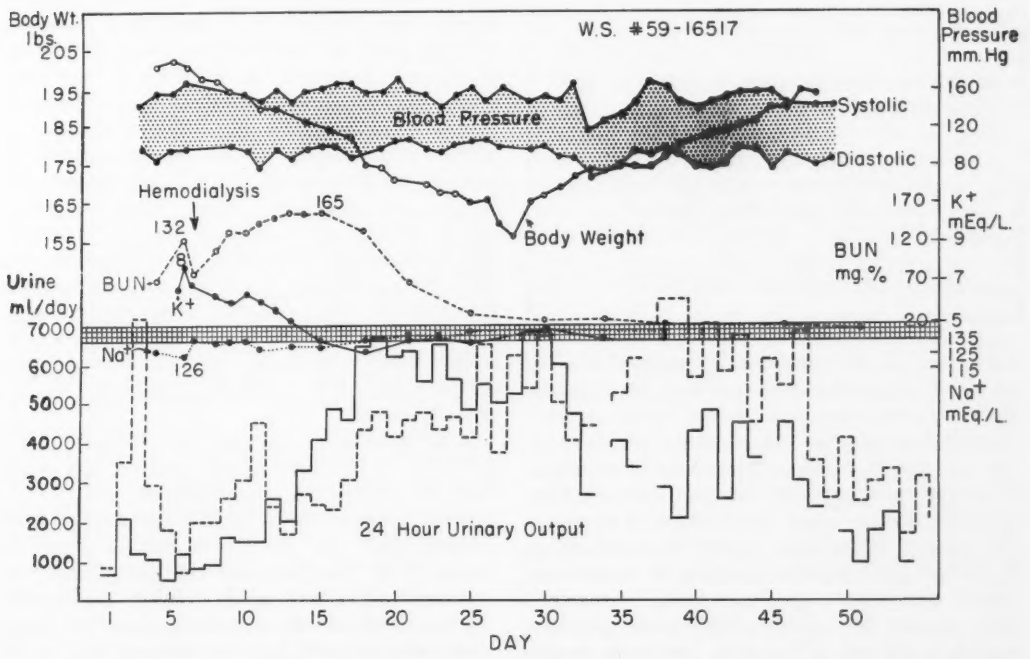

Figure 2. Patient S. W.: Solid line at the bottom of the graph indicates urinary output. Interrupted line indicates fluid intake.

Cholecystitis

Gallbladder Disease in the Geriatric Patient

W. G. CAUBLE, M.D., *Wichita*

CHOLECYSTITIS in the Geriatric patient can sometimes become a very serious and difficult problem. It is of such importance I thought it timely to present a series of cases found in my own practice and to discuss some of the salient points in caring for such patients. This series of 51 consecutive cases is a group of patients 65 years of age and older. It is small but probably represents a general picture of the problem as most of you and I see it. Since we are seeing and will see more elderly patients in the future, it behooves all of us to learn more about the care of them.

Many elderly patients have had gallbladder disease at intervals for years and some have been told that they had gallstones but either were not advised to be operated on or have failed on their own accord to seek surgical aid. A careful history on these patients will help considerably in making a diagnosis. In my own experience some have been unable to give a history themselves and it has been necessary to obtain it from relatives or friends.

In this series of 51 cases, 27 *(Table I)* had chronic cholecystitis. If this condition is suspected, we can use all of our usual ordinary methods of diagnosis. Many of these cases have cardiac disease or some other chronic condition and we should be able to get these patients in as good a general condition as possible prior to surgery. We can give them vitamins, especially vitamin C and other supportive treatment. I feel that it is important to keep them ambulatory as much as possible prior to surgery. In the ordinary chronic cholecystitis case, under usual circumstances, these patients do well. Walters regards operations on elderly patients with as little fear as on younger persons, provided the patients in question have been active until the onset of their illness. In this group, 27 were operated and only one died following surgery. This patient was 91 years of age and was operated on as an acute abdomen. He died of a pneumonia. The average hospital stay following surgery in these cases was ten and one-half days.

TABLE I

51 CONSECUTIVE CASES—CHOLECYSTITIS

65-91 YEARS
AVERAGE AGE 73
FEMALES—35 MALES—16
CHRONIC CHOLECYSTITIS—27
(Average stay in hospital—10½ days)
(one death)
ACUTE OR COMPLICATED CASES—24

It is the complicated case that concerns us mainly *(Table II)*. Several patients know that they have had gallstones for several years and then suddenly develop severe right upper abdominal pain. They may develop jaundice suddenly and seek medical aid. It is this type of geriatric case that develops into the severe problem, both from a diagnostic standpoint as well as from a treatment standpoint.

Acute cholecystitis should be differentiated from acute pancreatitis. It may be necessary to secure a serum amylase study at times. The serum amylase may be elevated some in gallbladder disease alone but it is usually greatly elevated in pancreatic disease. It may be advisable to think of an acute cardiac condition, pleurisy or pneumonia with upper abdominal pain and we may have to consult with our internal medicine friends. In elderly patients, coexistent cardiac or other diseases may be aggravated by acute cholecystitis.[12] Perforating or penetrating peptic ulcers may cause confusion and necessitate the taking of upright abdominal X-ray studies. Mesenteric thrombosis, intestinal obstruction, internal hernias, intussusception, volvulus, right kidney disease, or tabetic crisis should be thought of. Diverticulitis or rupture of a diverticulum of the hepatic flexure may simulate acute gallbladder disease. I recently had a case in which a diverticulum of the hepatic flexure had perforated and the colon was adherent to the liver. Prior to surgery I palpated a tender mass in the region of the gallbladder and thought that I was dealing with an empyema of the gallbladder. At surgery it was found to be a perforated diverticulum of the hepatic flexure and the gallbladder was essentially normal.

A flat plate of the abdomen will frequently reveal gallstones in the right upper quadrant and many times an intravenous cholangiogram will aid in showing gallstones in the gallbladder and a dilated common duct. An example of this is shown in *Figure 1*. In this particular case the patient was not jaundiced, in spite of the common duct pathology associated with the acute cholecystitis. Five large stones were removed from the common duct at the time of cholecystectomy.

Acute cholecystitis is generally initiated by a stone

TABLE II

ACUTE OR COMPLICATED CASES

Acute Cholecystitis All With Stones	*Jaundiced Cases*	*Primary Cancer of G.B.*
65—Emergency Cholecystostomy (did not return for removal)	C.D. explored in all T-tube	77, 81, 65—All with stones
72—Emergency Cholecystectomy	65—Stones in G.B. Fibrosis of C.D. (2 operations) Expired 2½ months after surgery	2—Cholecystectomy
70—Emergency Cholecystectomy	74—Died 5 days after surgery—Acute coronary	1—Cholecystostomy
70—Emergency Cholecystectomy Lower part left in	Pancreatitis Cholecystectomy	74—Carcinoma in situ (Ruptured) Living Cholecystectomy
87—Emergency Cholecystectomy Died of cardiac disease 3 months after surgery	91—Died 7 days after surgery Uremia Cholecystostomy	ASSOCIATED WITH OTHER CA
75—Emergency Cholecystostomy Associated with Ca of stomach	Removal of stones, C.D.	75—Acute Cholecystitis with Ca of stomach Cholecystostomy Gastroenterostomy (palliative)
86—Cholecystectomy Alive and well 5 years after surgery	81—Jaundiced with Ca, G.B. No stones in C.D.	88—Chronic Cholecystitis + stones Ca of head of Pancreas Cholecystogastrostomy
70—Cholecystectomy	72—C.D. stones—Living	BENIGN TUMORS OF G.B.
78—Cholecystectomy T-tube Alive 2 yrs. after surgery	78—C.D. stones—Living	72—Adenomyoma Cholecystectomy
72—Cholecystectomy	65—No C.D. stones—Living Apparently passed the stone	66—Multiple polyps Cholecystectomy
65—Cholecystectomy Exploratory of C.D. Abscesses of G.B. bed	TOTAL 7	
TOTAL 11		

impacted in the cystic duct,[1] but we must keep in mind that it can occur without stones in approximately five per cent of all cases.[2] Where there is a blockage of the cystic duct, this may lead to edema and thrombosis of the venous return and eventually arterial supply, with ischemic necrosis and early perforation. Because of the condition of the blood vessels in older patients, this condition advances with more rapidity and more violence. It is conceded by several writers[1, 3] that perforation and gangrene of the gallbladder is more common in older patients and certainly the mortality rate is higher in the older patient. Bartlett in reporting a series of 61 patients of various ages, reported five deaths in patients ranging from seventy to eighty-five years of age. These were the only deaths in the series. Hampson and others in discussing the white blood cell count in acute cholecystitis, state that the leucocyte count may be of value in assessing the individual case but serial counts are of even greater value in deciding on the possible need for emergency surgery. The differential count may also be useful since polymorphonuclear leucocytosis is the rule. Too much reliance on the level of the white cells in the circulating blood may, however, be dangerous as the acute process may go on to perforation in the presence of minimal leucocytosis. I feel that this is particularly true when caring for the elderly patient.

Because of the rapidity with which the condition may progress, it is advisable to treat the older patient somewhat differently than we would the younger patient. Ryan in reporting emergency operations in one hundred and three patients over seventy years of age, states that the age factor in mortality is twice as important as the emergency factor, which is itself large. Delay in seeing a doctor is common in the older patient and is certainly more lethal in older patients. The geriatric patient should be gotten into the best of condition and operated. Antibiotics should be given. We should try to replace electrolytes. If the patient is toxic or anemic, whole blood should be given slowly. It may be necessary to check on the blood volume and if it is low, blood replacement may be necessary. Overtransfusion is dangerous in the elderly patient and it is much safer to give small amounts (250 cc.) slowly, daily, than it is to give rapid replacement.[6] If the condition is subsiding the patient may be observed for twenty-four to forty-eight hours, but operation should not be delayed too long. A doctor should not be reluctant because of the patient's age, when at no age is delay more dangerous.[8] Avoid delay in diagnosis and treatment.

In this series where there was acute cholecystitis,

Figure 1. Intravenous Cholangiogram showing Gallbladder stones and dilated Common Duct.

two had cholecystostomy and nine had cholecystectomy. Certainly cholecystectomy is the treatment of choice if it is safe to do. If the anatomy is obscure around the cystic duct and vessels, it is much safer to do a cholecystostomy. It may be safer and wiser to even leave a part of the gallbladder in. This is particularly true if there is severe edema and inflammation involving the ampulla and extending onto the cystic and common ducts. In a few of these cases the clinical diagnosis of acute cholecystitis did not agree with the pathological diagnosis even when the patient had a leucocytosis and fever with other acute symptoms. This may be due to change from an infiltration of leucocytes to round cells or lymphocytes in the gallbladder wall. This may occur between the onset of the disease and the operation. In this manner the pathologist may see nothing to warrant a diagnosis of acute gallbladder disease.

One patient seventy-seven years of age was thought to have an acute cholecystitis and was operated on as an emergency. She had known she had gallstones for forty years and at operation, done under local anesthesia, an advanced carcinoma of the gallbladder was found. Removal of the stones and a cholecystostomy was done. Carcinoma of the gallbladder was found in four of the cases. All are dead except one in which a diagnosis of carcinoma in situ was made. This one case was ruptured at the time of operation. Preoperatively these were thought to be cholecystitis cases and all had stones. All but the one case had extension and metastasis at the time of surgery. The maximum rate of occurrence of carcinoma of the gallbladder as reported by Hardy is between sixty to sixty-nine years of age. Females are affected at a four to one rate over males. Tragerman in reviewing one hundred seventy-three cases of primary carcinoma of the gallbladder, found that it occurred most frequently between the ages of sixty-one to seventy. Seventy-nine and eight-tenths per cent of his cases had stones. In view of this we should keep this diagnosis in mind when operating an elderly patient for gallbladder disease. This is especially true if the patient has lost weight. Polyps of the gallbladder should be thought of. One *(Figure 2)* was found in this series. It has been shown that sometimes carcinoma can occur in

Figure 2. Polyps of the Gallbladder.

papillomas.[11] Other benign tumors may occur such as adenomyoma found in one case *(Figure 3)*.

Seven patients in this series were jaundiced at the time of surgery and operation was imperative. One case was of particular interest in that her jaundice was caused by extensive fibrosis from the gallbladder and cystic duct extending onto the common and into

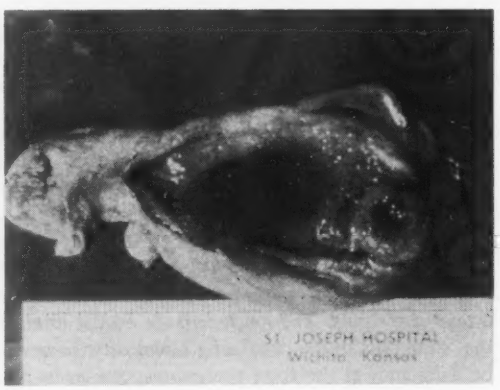

Figure 3. Benign Adenomyoma of the Gallbladder.

the hepatic ducts. No stones were found and biopsies revealed no carcinoma. This patient pulled her T-tube out and had to be re-operated. She later died two and one-half months after her original surgery. Four of these patients had common duct stones and two of these are living and well. One was jaundiced from a primary carcinoma of the gallbladder. One with common duct stones died four days postoperative, of an acute coronary attack proven at autopsy, and the other died of uremia seven days after surgery. It is shown by these cases that the elderly patients do not tolerate common duct surgery too well. It adds so much more to the operation. Walters states that the risk of cholecystectomy is increased three fold for the patient who is jaundiced or when stones are removed from the common bile duct.

One case, seventy-five years of age, had acute cholecystitis associated with carcinoma of the stomach and at operation a cholecystostomy and a palliative gastroenterostomy was carried out. He expired four days after surgery. Another case, eighty-eight years of age, with a carcinoma of the head of the pancreas had a chronic cholecystitis with stones. A cholecystogastrostomy was carried out. He expired twenty-one days following surgery.

Summary

In summary, fifty-one cases of gallbladder disease in patients sixty-five years of age or over have been presented. A preoperative diagnosis of cholecystitis was made in practically every case. There was one postoperative death in those having chronic cholecystitis and there were eight deaths in those having acute cholecystitis or other complicating condition including cancer. The diagnosis of acute cholecystitis has been discussed and early operation has been urged. It has been shown in this series that common duct surgery is not tolerated too well by the elderly patient. If at all possible the patient should have the best of preparation prior to surgery and with good anesthesia these patients will do well under ordinary circumstances. Cases with primary carcinoma of the gallbladder and those associated with other carcinomas have presented. Two cases with benign tumors of the gallbladder have been included. It is granted that this is a small number of cases but these reveal some very interesting pathology. In my own practice, I tell the patient with gallstones that it is like carrying around a stick of dynamite and it may explode anytime. Certainly many of these cases reveal such an explosion.

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Hemodialysis

(Continued from page 473)

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Iodide Goiter

Report of a Case

DAVID LUKENS, M.D., ***Hutchinson***

The unusual syndrome of iodide goiter and myxedema is described and a case of goiter with myxedema following prolonged administration of potassium iodide is presented. Similarities and discrepancies with respect to previously described cases are discussed. Intermittent therapy of patients requiring long term administration of iodides may be helpful in the prevention of this disease.

THE OCCURRENCE of myxedema or goiter following prolonged administration of iodine has aroused increasing interest in recent years, and since 1945 more than 40 cases of this syndrome have been reported. The inhibition of hyperfunction and involution of a toxic goiter by exogenous iodide has been generally accepted since 1923. Although experimental evidence suggests that large doses of iodide may suppress thyroid hormone synthesis in the normal gland, this effect is transient and disappears after 26 hours. Nevertheless an occasional patient will develop goiter or myxedema after iodide treatment, and it is the purpose of this presentation to call attention to this rather unusual drug induced disease.

Case Presentation

The patient is a 36 year old female who was first examined on November 22, 1959, because of abdominal pain and severe constipation. She had suffered from bronchial asthma for 25 years, and she gave a vague history of a goiter at age 16, although thyroid enlargement was not confirmed by medical observation. In 1952 she was examined in an asthma clinic elsewhere and was given a cough medicine containing digitalis, potassium iodide and Fowler's solution. For six years she took this medication, containing potassium iodide 780 mgm. per day, and her asthma seemed definitely improved. Two years prior to our examination she experienced the insidious onset and gradual progression of crampy abdominal pains, severe constipation, cold intolerance, dryness of the skin and hair, lack of energy and hoarseness. Physical examination revealed pulse 88; blood pressure 130/85. The patient was adequately nourished, but the complexion was pallid, and her voice was quite hoarse. There was definite periorbital edema and her skin and hair were coarse and dry. The thyroid gland was firm and diffusely enlarged three times normal size, with no thrills or bruits demonstrable. The abdomen was distended and protuberant, but no masses or enlarged organs were palpable. The deep tendon reflexes were hypoactive bilaterally at the biceps, triceps, and knees. Ankle jerks were not obtainable by any method.

Preliminary laboratory data are as outlined in Table I. On January 15, 1960, thyroid biopsy was performed. Histologically the gland showed changes characteristic of hyperplasia with an increased number of follicles, prominent vascularity, and papillary infoldings of the epithelium which was generally tall and columnar. The colloid content was sparse, and in some areas where follicles were small and crowded, no colloid was identifiable. Following discovery of a hyperplastic goiter, exogenous iodide was discontinued. It was anticipated that the patient would return rapidly to the euthyroid state, but two months after iodide withdrawal clinical evidence of myxedema was unchanged, and the thyroid enlargement persisted. Repeat I^{131} uptake showed no improvement, and she was given Cytomel 25 mcg. daily beginning

TABLE I

Serology	Non-Reactive
Hemoglobin	12.2 gm%
Hematocrit	39%
WBC	8,550
Differential	Normal
Urine	Clear, 1.002, Alb, Sugar, Micro Negative
FBS	95 mgm%
NPN	31.5 mgm%
Sodium	142 mEq/L
Potassium	4.7 mEq/L
CO_2	24.0 mEq/L
Chloride	119 mEq/L
BMR	+1
PBI	Contaminated with Iodine
RAI Uptake	7% in 6 hours, 3% in 24 hours
Chest X-ray	Normal
Skull X-ray	Normal
Arsenic (Hair & Nails)	3 mgm/100 gm

Originally presented to the regional American College of Physicians meeting, March 3, 1961.

March 22, 1960, increasing to 37.5 mcg. daily on May 26, 1960. In July, 1960, the thyroid gland returned to normal size; by September, 1960, all signs of hypothyroidism had disappeared, and the patient assumed full time gainful employment in addition to caring for her home and family.

Table II shows the serial radio iodine uptake studies. On February 6, 1961, the BMR was +18, Cholesterol 213, and the PBI was still greater than 30 mcg. per cent.

The original clinical diagnosis was Hashimoto's Thyroiditis, but after the thyroid biopsy it was apparent the patient had iodide goiter with myxedema. The diagnosis of chronic arsenic intoxication was considered briefly, but this seemed to be excluded by the demonstration of only minute amounts of arsenic in her tissues. Certainly her response to iodide withdrawal and thyroid hormone replacement is typical of all previously reported cases, although she did not show the rebound thyroid hyperactivity observed in many of these patients.

TABLE II

RADIOACTIVE IODINE UPTAKE

Date	*Clinical State*	*Uptake* 6 hrs.	24 hrs.
12/21/59	Myxedematous On KI Thyroid 3X normal	7%	3%
3/18/60	Myxedematous Off KI 2 mo. Thyroid 2X normal	5%	3%
11/28/60	Euthyroid On Cytomel 8 mo. Thyroid normal	7%	2%

The clinical picture of this syndrome is that of myxedema or goiter, or both, developing in an otherwise euthyroid patient who receives iodide in large doses over a prolonged period of time. The mechanism by which iodine exerts its depressing effect on normal thyroid function is not yet well understood. Most observers agree that excess iodide blocks organic binding of iodine on the thyroid gland, although there is evidence[24] that the interaction of thyrotropin and excess iodide promotes suppression of thyroid hormone secretion. Inhibition of I^{131} uptake by small amounts of stable iodine[16] is a characteristic finding in iodide goiter, and the similarity of response to this inhibition between hyperthyroid patients[25] and those with iodide goiter is unmistakable.

The histology of iodide goiter is variable. In 12 patients subjected to surgery, four[2, 4, 11, 17] had colloid storage goiter, one[6] had struma lymphomatosa and seven[7, 15, 16] showed epithelial hyperplasia. The evidence indicates that iodine, in some normal thyroids, produces involution with colloid storage, but in a majority of cases hyperplasia is more typical. It therefore becomes necessary to distinguish between patients with previously normal thyroid glands, and those with some underlying thyroid disorder, in whom myxedema or goiter appears secondary to iodide administration. Bell[11] has suggested the following classification:

1. Patients with small amounts of hyperactive thyroid tissue, that is, with mild Graves' disease, either primary or recurrent following remote thyroid surgery.

2. Patients with low reserve thyroid glands: Graves' disease immediately following surgery or I^{131} treatment and apparently euthyroid; chronic thyroiditis; and nontoxic hyperplastic goiters with defective hormone synthesis.

3. Some apparently normal euthyroid individuals.

The present case appears to be an example of iodide goiter in a patient with defective hormone synthesis, or with inhibition of organic binding by small amounts of circulating iodide over a long period of time, from which effect she is unable to "escape." Lack of facilities prevents a more precise classification of this patient's physiological defect, however, it is reasonable to assume that her thyroid can trap iodine, but is incapable of organic binding. As to why radioiodine uptake remains low for many months following withdrawal of exogenous iodide, one can hypothesize[26] the presence of a depot of organic iodine, slowly releasing iodide at a level high enough to block organic binding in the thyroid gland.

An increased awareness among physicians of the iodide myxedema syndrome will undoubtedly lead to the future recognition of many more new cases. Biopsy of the thyroid gland in all suspected iodide goiters will be an important contribution to the precise diagnosis of this condition, helping to differentiate it from Hashimoto's thyroiditis and other unrelated disorders, although further study will be required to delineate the exact pathogenesis of iodide inhibition of normal thyroid function. In those patients with cardiorespiratory diseases requiring prolonged administration of iodide, intermittent therapy, with or without simultaneous administration of thyroid extract, may be helpful in preventing the appearance of myxedema or goiter.

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Intractable Heart Failure

Case Presentation

THIS 46-YEAR-OLD white housewife was in an unresponsive state when she was admitted to KUMC for the first time on April 10, 1959.

For about four years before admission she had had swelling of her legs, but she had been considered to be in fairly good health until eight weeks before admission when she began to complain of nausea and weakness. These symptoms continued for about one week, and she was hospitalized elsewhere. At that time the liver was large, and there was yellow discoloration of both periorbital regions. She had upper abdominal pain and dyspnea which was markedly increased by slight exertion. After five weeks in the hospital she improved slightly and she was permitted to take thirty minute automobile rides. Three days before admission, however, she could no longer tolerate the rides. Two days before admission she developed a cough, and on one occasion dark blood appeared in the sputum. The upper abdominal pain became more severe, and her condition became progressively worse. She went into a shock-like state and was unresponsive on the afternoon of admission when she was flown here for further evaluation.

She had had occasional convulsive seizures since childhood, but these had been well controlled by drugs. She had had a cesarean section at term of her pregnancy, the date of which is unknown, but the child died shortly after birth.

Her father died of a heart attack at 63 years of age.

The patient was a well developed, thin, cyanotic, white woman who did not respond to any stimuli. The apical pulse rate was 160 per minute; respiration, 46 per minute. Her temperature was not recorded, and her blood pressure was not obtainable. The conjunctivae were pale, and there was no scleral icterus. The pupils were small but reacted to light, and the optic fundi were normal. There was cervical venous distention. The thyroid was diffusely enlarged, soft and non-nodular. There were dullness and decreased breath sounds at both posterior lung bases. Rhonchi and crepitant rales were heard throughout the lung fields. The cardiac rhythm was irregular, and the heart tones were diminished. The second pulmonic sound was louder than the second aortic sound. There were no murmurs. There was a midline scar from the umbilicus to the pubis, the abdomen was distended, and there was a fluid wave. The liver was smooth and enlarged to 11 cm. from the right costal margin and 7 cm. from the left costal margin. One observer palpated the spleen. The femoral, radial and ulnar pulses were not palpable. The patient's feet and hands were cold and deeply cyanotic; there was no clubbing of the fingers. Dupuytren's contractures of the left third, fourth and fifth fingers were present. Grade IV pitting edema was present in both legs and feet, and the left leg was larger than the right. The deep tendon reflexes were absent. There was no Babinski sign.

The patient continued to have tachycardia and tachypnea, and her blood pressure could not be obtained. She died quietly about five hours after admission.

Dr. Mahlon Delp (moderator): Are there any questions?

John Hutcherson (student*): Will you describe the apex beat and its location?

Dr. Delp: The apex beat was neither visible nor palpable.

Dr. Bert Lum (student): Will you describe the auscultory findings in the chest?

Dr. Delp: Numerous rales were heard throughout the right lung posteriorly and in the upper half of the left lung. There was no dullness on the right.

Edited by Jesse D. Rising, M.D., and Mahlon Delp, M.D., from recordings of the proceedings of the conference participated in by the departments of medicine, pediatrics, surgery, radiology and pathology of the University of Kansas Medical Center as well as by the third and fourth year classes of students.

* Although a student at the time of this conference in January, 1960, he, like the others referred to as students, received the M.D. degree in June, 1960.

Breath sounds in the lower half of the left lung were markedly diminished or absent. The whole left lower lung was probably dull to percussion. Respiration was rapid and shallow.

Carl Dahl (student): Was the lateral abdominal pain localized to one side or the other?

Dr. James W. Davis (resident in medicine): There was bilateral abdominal pain.

Mr. Dahl: Was there evidence of hematuria?

Dr. Davis: No.

George Hubert (student): Was leg tenderness ever reported?

Dr. Delp: It had not been reported because the patient was unresponsive on her arrival here, but it had been noted before.

Mr. Hutcherson: When did she go into coma?

Dr. Delp: Her local doctor said that she had been hospitalized for about five weeks because of liver disease. Several minutes before his call here at 4:00 p.m. she had become pulseless, and he could not obtain her blood pressure.

Mr. Dahl: Was there a hepato-jugular reflex?

Dr. Delp: Yes.

Mr. Hubert: Was orthopnea reported?

Dr. Delp: Orthopnea was apparently not a feature of her difficulty as she had been able to sleep quietly all during her hospitalization.

L. Borgendale (student): Was there a definite line of demarcation between her cold extremities and the rest of her body?

Dr. Davis: No.

Mr. Hubert: Was there any visible collateral venous circulation of the chest?

Dr. Davis: No, there was not.

Dr. Lum: Was there a record of low-grade fever during her hospitalization elsewhere?

Dr. Delp: No. If she had had fever it apparently was low-grade and not an important part of her signs or symptoms because it was not recorded.

Mr. Hutcherson: Was any change made in her anticonvulsant medication?

Dr. Delp: She had been receiving medication for some time, and no changes had been made in them.

Dr. Wallace McKee (internist): Was the swelling of her legs which she had had for four years very marked?

Dr. Delp: It was a grade III or IV plus edema.

Dr. Lum: Did her local doctor state the cause of the edema?

Dr. Delp: No.

Dr. Lum: Did the patient complain of dyspnea?

Dr. Delp: Her husband said that she had not really complained of dyspnea on exertion, but I interpreted his description of her activities as indicating that she had become tolerant of her dyspnea, and consequently did not complain of it.

Mr. Dahl: Was a urinalysis reported?

Dr. Delp: No, a urine specimen was not obtained.

Mr. Hutcherson: Did she have a history of orthopnea and nocturnal dyspnea?

Dr. Delp: No, she did not.

Dr. Lum: Was the liver smooth?

Dr. Delp: Yes.

Dr. McKee: What was her blood pressure before her hospitalization?

Dr. Delp: It was normal.

Mr. Borgendale: Was there anything unusual about the jugular venous pulse?

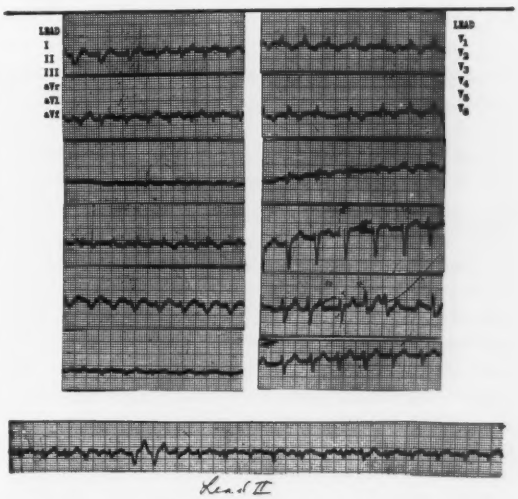
Dr. Delp: It was not a strong pulse.

Dr. Lum: Were any urinalyses taken before she was hospitalized here?

Dr. Delp: Yes, and I understand that they were negative. May we have the electrocardiogram now, please?

Electrocardiogram

Mr. Borgendale: The only electrocardiogram *(Figure 1)* of this patient was taken on the day of admission which was also the day of death. It is an abnormal tracing showing a ventricular rate from 120 to 150. There is evidence of P wave activity and normal P-R interval. There is a S_1 wave in lead I and Q_3 wave in lead III. The electrical axis is perpendicular to lead III and aVf making a positive plus 50 electrical axis. Over the chest there is an upright R in lead V_1 and an rsR in lead V_2 and V_3 with a QRS interval of about 0.10 of a second. Non-specific T wave inversion is seen in leads V_1, V_2 and V_3. The transition zone is markedly delayed, occurring between V_5 and V_6. I interpret these changes as compatible with an incomplete right bundle branch



EKG: 1. Electrocardiogram made the day of admission.

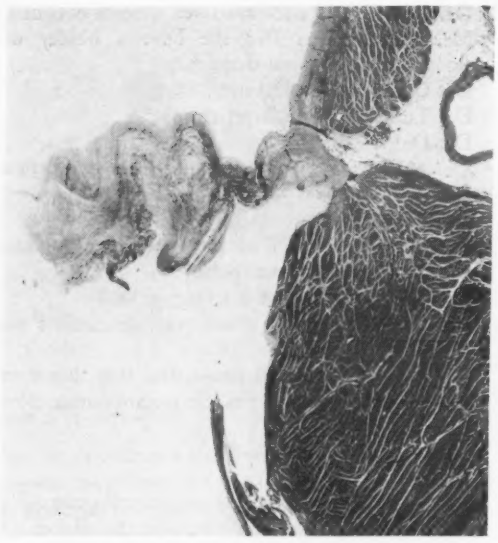


Figure 1. The mitral valve is thickened and retracted. H and E. Green filter. ×6.5.

block and suggestive of acute cor pulmonale with evidence of paroxysmal tachycardia and clockwise rotation of the heart.

Dr. Delp: Thank you. There are no x-ray studies on our patient, so we will now have the discussion.

Differential Diagnosis

Dr. Lum: This 46-year-old white woman was admitted here with a four-year history of swelling of the legs. Eight weeks before that she had been hospitalized elsewhere because of weakness and nausea, and at that time she had hepatomegaly, dyspnea and upper abdominal pain. Two days before admission here she developed a cough and hemoptysis; and she later became unresponsive and went into shock. Physical findings at that time included tachycardia, tachypnea, irregular heart beat, absence of peripheral pulses, cervical venous distention, hepatomegaly and peripheral edema. She died five hours after being admitted.

My differential diagnosis is based on the causes of intractable heart failure in a middle-aged woman. There is no reason to suspect such common causes of heart failure as hypertensive, coronary and valvular heart diseases because these diseases usually present with an early onset of pulmonary congestion which is not seen here. Pulmonary and tricupsid valvular lesions often lead to right heart failure as manifested by our patient. The presence of shock may have masked a murmur, but there was no history of a murmur. In addition, right valvular lesions are usually associated with left valvular lesions. Congenital heart disease rarely manifests itself in later life, and the lack of any positive supporting evidence in the patient's history and physical findings makes this diagnosis untenable.

Collagen diseases sometimes produce heart failure, but are usually associated with multiple organ manifestations. There is no evidence here to support a diagnosis of hematopoietic disorders such as anemia.

Vascular disorders such as an arteriovenous fistula must be considered, but no murmurs or thrills were reported. Obstructive lesions of the inferior vena cava do not produce cervical venous distention. Primary neoplasm of the heart, such as fibroma, rhabdomyoma and sarcoma are extremely rare and have a rapid,intractable course. Myomas are slightly less rare, but are usually found in the left atrium. Murmurs and symptoms of marked pulmonary congestion are present. Metastatic lesions of the pericardium and myocardium can be ruled out because of the absence of a demonstrable primary site.

The presence of an enlarged thyroid suggests the possibility of thyrotoxic heart disease, but because of the lack of associated findings of thyrotoxicosis, I shall dismiss it as a primary diagnosis. Myxedema and other endocrinopathies can be discarded for the same reason.

Diseases producing chronic cor pulmonale such as emphysema, asthma, bronchiectasis, sarcoidosis, and the granulomatoses are unlikely because of the lack of supportive clinical and historical evidence. Primary pulmonary hypertension is manifested by exertional dyspnea, weakness, exertional precordial pain and syncope, and these symptoms usually appear early in the course of the disease. Cor pulmonale due to pulmonary embolization could be a possibility later in her course, but it is an unlikely primary diagnosis of the early failure observed.

The most common myocarditides such as those associated with infection, toxic agents and hypersensitivity reactions may be ruled out because of the lack of clinical history. A more attractive diagnosis is that of endomyocardial fibrosis which rarely presents with predominantly right heart failure because of involvement of the right ventricle. The course of the disease may vary from one month to several years duration often with minor symptoms. At times the picture is that of early left heart failure.

Another possible diagnosis is chronic constrictive pericarditis. Findings compatible with that diagnosis are effort dyspnea, hydrothorax, ascites, edema of the ankles and legs, palpitation, weakness, hepatomegaly with abdominal discomfort, cervical venous distention, nausea and vomiting. The second pulmonic sound is greater than the second aortic sound, and there are rales, an irregular cardiac rhythm cyanosis, and a palpable spleen. All of these signs and symptoms were found in our patient, and all are characteristic of constrictive pericarditis.

Under the category of metabolic heart disease hemachromatosis is an unlikely diagnosis because of

the absence of bronze diabetes. Xanthomatosis, glycogen storage disease, fatty infiltration of the heart, and toxic agents can be ruled out because of the lack of history and clinical evidence. There is no evidence of a chronic suppurative disease such as tuberculosis to support the diagnosis of secondary amyloidosis. Amyloid may be virtually localized to the heart in primary cardiac amyloidosis, but that form of the disease has been found only in patients over 60 years of age.

Primary systemic amyloidosis is characterized by the deposition of amyloid in mesodermal tissue, the cardiovascular system, the gastrointestinal tract, lymph nodes, and in smooth and striated muscles. There is minimal deposition in the liver, spleen, kidneys and adrenals which, in contrast, these are sites of maximal deposition in secondary amyloidosis. Cardiac involvement is found in 80 per cent of the cases of primary systemic amyloidosis at autopsy, and is sufficient to produce congestive failure in 50 per cent of the cases. Death occurs in about 40 per cent. In primary systemic amyloidosis there may be clinical findings of macroglossia, nodules or plaques in the skin and buccal mucosa and other skin lesions, lymphadenopathy and purpura. It has been reported, however, that in 50 per cent of the cases with congestive failure there was clinical evidence of myocardial damage alone. There have been no reported cases of recovery from primary amyloidosis. The course of the disease is extremely variable, and the average survival period is 32 months. The longest surviving patient lived for 14 years.

Heart failure can result from a variety of amyloid lesions such as diffuse or nodular myocardial deposits, infiltration of the visceral pericardium or endocardium and involvement of the valves of coronary arteries. Combined lesions occur and give rise to complex clinical pictures. In some cases constrictive pericarditis may be closely mimicked by amyloidosis of the heart resulting in restriction of myocardial contraction and relaxation. As in the case of other rare or atypical diseases, the diagnosis is largely a matter of awareness of the possibility of systemic amyloidosis.

In summary, I believe that our patient had primary systemic amyloidosis. Early in her course cardiac involvement produced a relatively mild right heart failure with subsequent progression, and severe symptoms developed eight weeks before death. At that time amyloid infiltration of the lungs and also a relatively silent pulmonary embolization could have been contributing factors. I believe that terminally there was massive, multiple pulmonary embolization which resulted in hemoptysis, shock and death. Enlargement of her left leg suggests that the emboli may have originated from the veins in that leg.

Clinical Discussion

Dr. Delp: Thank you, Dr. Lum. What is your primary diagnosis, Mr. Hutcherson?

Mr. Hutcherson: Chronic constrictive pericarditis terminating with acute cor pulmonale as a result of embolization.

Dr. Delp: Mr. Hubert?

Mr. Hubert: Primary amyloidosis.

Dr. Delp: Mr. Dahl?

Mr. Dahl: Chronic constrictive pericarditis and pulmonary embolus.

Mr. Borgendale: I believe she had endomyocardial fibroelastosis with mural thrombi which are commonly found in that disease and which, in turn, resulted in numerous episodes of embolization.

Dr. Delp: How do you explain the vascular collapse which apparently occurred during her five weeks of hospitalization, Mr. Hutcherson?

Mr. Hutcherson: It could be explained on the basis of pulmonary embolization leading to shock and coma.

Mr. Borgendale: She could have had previous episodes of pulmonary embolization and, finally, a cerebral embolus from a mural thrombus.

Dr. Delp: Five weeks before her admission here her local doctor found that her liver was enlarged, and at that time it was his impression that she was jaundiced. How do you explain that, Mr. Hutcherson?

Mr. Hutcherson: Hepatocellular damage can occur in congestive failure and engorgement of the liver. I do not believe, however, that that was of any significance in her clinical course.

Mr. Dahl: Amyloid may produce yellow papules and plaques, but I doubt that it would produce jaundice. If she had jaundice it probably was because of hepatocellular damage.

Dr. Delp: Mr. Borgendale, do you believe that the patient had pulmonary emboli five weeks before her admission here and before her original hospitalization elsewhere?

Mr. Borgendale: Jaundice is often associated with pulmonary emboli, and that could have been the reason for her first complaint of dyspnea.

Dr. Delp: How do you account for the fact that she did not have orthopnea, Mr. Hutcherson?

Mr. Hutcherson: It is compatible with constrictive pericarditis because there is no pulmonary flow to produce pulmonary congestion.

Dr. Delp: Mr. Hubert?

Mr. Hubert: Initially she probably had right heart failure which does not give rise to pulmonary congestion.

Mr. Dahl: Constrictive pericarditis limits the increase in output. Perhaps she only had slight tachycardia and dyspnea on exertion.

Mr. Borgendale: Endomyocardial fibroelastosis can cause the same physiological changes as those found in pericarditis.

Dr. Delp: There is a paucity of auscultory findings of the heart mentioned here. What other auscultory

findings would you have wanted to hear, Mr. Hubert?

Mr. Hubert: I would have tried to hear a friction rub.

Dr. Delp: Mr. Dahl?

Mr. Dahl: Shock could have been the reason for not hearing the murmur.

Dr. Delp: Dr. Crockett, may we have your discussion, please?

Dr. James E. Crockett (cardiologist): It has been carefully pointed out that our patient appears to have had right heart disease. She did not have orthopnea, and apparently exertional dyspnea was not a significant symptom until late in her course. She had no past history of left heart disease of any type that we would be likely to diagnose. An interesting fact is that she had had swelling of her legs for four years before admission, but she was apparently considered to be in good health until about eight weeks before admission when nausea and weakness developed.

The question arises as to whether or not she had had severe vericose veins with dependent edema for several years. She was believed to be in good health, apparently, because her symptoms were recognized and not considered to be serious problems. She probably went into right heart failure, however, about eight weeks before admission, although we can not be certain of this sequence. At any rate there was a significant change in her illness about eight weeks before admission, and it must be assumed that it was either the onset of right heart failure or an intensification of right heart failure. In my opinion the electrocardiogram shows right ventricular hypertrophy rather than right bundle branch block. I believe that there was a QR wave over the right precordium rather than an rsR as would be expected. I am uncertain about the arrhythmia which was present, and although it seemed to be atrial in origin, I am not sure that it was an uncomplicated atrial tachycardia. This could represent a form of paroxysmal atrial tachycardia. It would be interesting to know whether the patient had received digitalis.

Dr. Delp: We do not know whether or not she received digitalis before her admission here.

Dr. Crockett: It seems to me that a patient with such a clinical picture must have been receiving some digitalis. She was probably acutely cyanotic for a while, but patients in such a situation become sensitive to digitalis. If her doctor became apprehensive and began to push digitalis it would be a perfect clinical situation for digitalis intoxication and this particular arrhythmia which is so frequently associated with digitalis intoxication. Constrictive pericarditis would certainly have to be considered. I am somewhat concerned about the length of the patient's illness. It is my assumption that the swelling of her legs was not related to cardiac disease.

Carcinoid syndrome must be mentioned here with the well-recognized involvement of the tricuspid and pulmonary valve. The absence of murmurs does not particularly disturb me because she did not have an obtainable blood pressure. The blood was not coursing vigorously through the heart, and dynamic findings could have been altered considerably with the result of complete loss of pulmonary systolic murmur secondary to pulmonary stenosis.

It is my impression that the patient had had pulmonary embolization and thrombophlebitis for an undetermined period of time, and we are actually seeing here the Castlemen-Bland syndrome. I believe that her right heart failure was secondary to this condition, and that the terminal episode was probably related to a massive pulmonary embolism. I am impressed by the fact that she had a cough, and on one occasion had brought up dark blood in her sputum. Her left leg was larger than her right, but there was bilateral edema. I believe that the terminal episode was a massive pulmonary embolus producing the shock state, and the absence of auscultory findings may have been related to the serious degree of shock and failure which was present. We might have anticipated hearing a third or fourth sound. She certainly had a loud pulmonic second sound which would be associated with either acute or chronic cor pulmonale.

Dr. Delp: Thank you. May we hear from you now, please, Dr. Rankin?

Dr. Thomas J. Rankin (internist): My one definite impression is that the patient did not have the terminal heart failure of gargoylism because she was not described as having a gargoyl-like face. The most significant thing to me is her long-standing history of a mild, relatively symptomless edema of the legs which definitely points to a chronic background to the disease from which she died. It seems that the alternatives are four: (1) she began with a primary cardiac disease of right-sided origin; (2) she began with primary hepatic disease; (3) she had thyroid disease, the thyroid being diffusely enlarged; (4) the Depuytren's contractures of the fingers of her left hand suggest that she could have had a shoulder-hand phenomenon as a result of acute and asymptomatic coronary damage. She could also have had a low grade chronic granulomatous disease of the liver which was not an active process, and the edema which she had for four years may have been due to that. Some observers agree that the spleen was enlarged and palpable, and, in my opinion, that adds to the possibility. If one supposes that disease in the liver did exist as part of her approach, however, in order to explain the total events one would be compelled to say that she was tuberculous and return to the opinion formed by the students that she also had a constrictive pericarditis of tuberculous origin. If such were the case the suddenness of change from chronic edema of the

lower extremities to a terminal illness could induce such phenomena as Budd's cirrhosis.

If hepatic disease is considered as the background of these symptoms one must also consider the low grade persistent chronic hepatitis which is sometimes without symptoms. At autopsy it is sometimes believed to have existed with no suspicion on the part of the physician. Dr. Crockett explained the terminal cardiac findings by multiple embolizations from the edematous lower extremities and right heart failure at the conclusion of the picture. My diagnosis, however, is constrictive pericarditis.

Dr. Delp: Thank you. May we have your opinion, Dr. McKee?

Dr. Wallace McKee (internist): The most significant thing to me is the onset of the relation between the edema and the liver difficulties. The liver was enlarged on admission, and before that she had had edema. She had a hepato-jugular reflex which suggests that she may have had tricuspid valve insufficiency. It is entirely possible for an individual to have tricuspid valve insufficiency for several years and still not have too much difficulty with respiration. I assume that the enlarged liver and spleen, edema of the legs, and the tricupsid insufficiency were all present for a period of four years. There is evidence that she had pulmonary hypertension, and the question arises whether it was acute, chronic or subacute. I assume that it was present for a long time together with evidence of right heart enlargement and the increased pulmonary second sound. As a differential diagnosis of pulmonary hypertension the collagen disease, perhaps, has not been mentioned sufficiently. Periarteritis and lupus erythematosus can cause pulmonary hypertension, and these, plus the granulomatous diseases can cause a considerable amount of respiratory distress in association with the failure that might ensue. The respiratory distress is usually rather striking at first. At the other end of the lung the left side of the heart can cause difficulty. A diagnosis of mitral stenosis was not made because there were no murmurs, but I believe that the lack of murmurs is insignificant because of reasons already mentioned. The patient apparently had a normal blood pressure. I must forego the diagnosis of constrictive pericarditis. There was probably a tight non-audible mitral stenosis with pulmonary emboli and pulmonary thrombotic phenomena occurring later. I do not know whether this was embolization or thrombosis. The yellowish discoloration which is frequently found with pulmonary embolization was present.

Dr. Delp: Thank you. Dr. Dunn?

Dr. Marvin Dunn (cardiologist): The fact that this patient was a well developed and well nourished woman makes me disfavor the diagnosis of systemic disease for more than four years. If this were an hepatocellular disease of that duration I certainly would have anticipated some muscle wasting at that stage of the disease. In my opinion the most significant physical finding is the loud second sound, and the other positive finding is the electrocardiogram which, as Dr. Crockett has pointed out, shows a QR complex at the V_1 and V_2 positions. The combination of these two findings suggests a disease that had produced pulmonary hypertension over a long period of time rather than an acute episode of pulmonary hypertension. The other possibilities, atrial septal defect and ventricular septal defect, certainly could live to this age and gradually develop pulmonary hypertension. I would have expected, however, that the last few years of the patient's life would have been associated more with cardiovascular symptoms than seem to be apparent here.

Primary pulmonary disease is another diagnosis that has not been emphasized. Castlemen-Bland syndrome has been mentioned, and I believe that it would be more compatible with the patient's general clinical course than some of the other suggestions that have been made. I believe that the patient had either Castlemen-Bland syndrome or primary pulmonary disease resulting in right heart failure and cor pulmonale, and that the terminal event was massive pulmonary embolus.

Dr. Delp: Thank you, Dr. Dunn. May we have your report now, Dr. Klionsky?

Pathological Report

Dr. Bernard Klionsky (pathologist): Major findings were in the heart and lungs. The heart weighed 340 grams and showed a moderate rheumatic mitral stenosis with fibrosis, adhesions and contracture of the valve and of the chordae tendineae. The orifice which measured 1½ cm. in diameter, was not tightly sclerotic. The left atrium and right ventricle were hypertrophied. Mural thrombi were present in the left and right atria. A section of heart shows a thickened mitral valve *(Figure 2)* shortened, thick chordae tendineae with adhesions between the valve and the papillary muscle.

Thromboses were present not only in the left iliac but in the left ovarian vein *(Figure 3)*. Ovarian veins are frequently the source of thrombi and emboli. The thrombi were organizing at the periphery, but were fairly fresh centrally. If a recent embolus had occurred from some of this fresher central area, there would be no way microscopically of detecting it as thrombus. A fresh blood clot in the pulmonary arteries would be all that would be found. There were a number of vessels in the lung where one could see blood clots both grossly and microscopically, but none could be proved to be of a definite ante mortem status. No older emboli were present, but there were some areas of hemorrhage, particularly in the right lower lobe, and some areas of actual infarction.

Figure 2. Ovarian vein is filled by a laminated thrombus. H and E. Green filter. ×12.

The left lung showed a different process. There was 3,000 ml. of fluid in the left thorax, and the left lower lobe was completely atelectatic. Multiple nodules were noted grossly in the vicinity of bronchi and blood vessels in the left upper lobe only. There were a few relatively fresh thrombi in small branches of hepatic veins, and there were some areas of fresh necrosis within the liver, presumably caused by a combination of venous stasis and systemic shock. There were no older lesions within the liver to explain the previous jaundice. The relatively slight degree of congestion in the liver might suggest that heart failure was not advanced and that the edema in the extremities may have been related, at least in part, to the venous thromboses.

The lymph nodes *(Figure 4)* and the peripheral areas of the lung contained multiple granulomatous nodules, usually discrete, occasionally confluent. No caseation was present; histiocytic giant cells were found. High power views of a granuloma and giant cells showed some suggestive inclusions which could not be identified. The morphology is consistent with the diagnosis of sarcoidosis. Multiple sections were stained with auramine-rhodamine and examined under the fluorescent microscope for acid-fast bacilli. Special stains for tubercle bacilli, fungi and bacteria were negative. Polarizing microscopy revealed a small amount of silica at the periphery of anthrocotic nodules. The quantity of silica is not sufficient to produce the granulomas. There was no crystalline material to suggest berylliosis.

Granulomatous nodules which were found in the left atrium of the heart *(Figure 5)* have been described in approximately 20 per cent of cases of sarcoid. It is believed that they tend to follow the bronchi and pulmonary veins to the hilar area of the lung

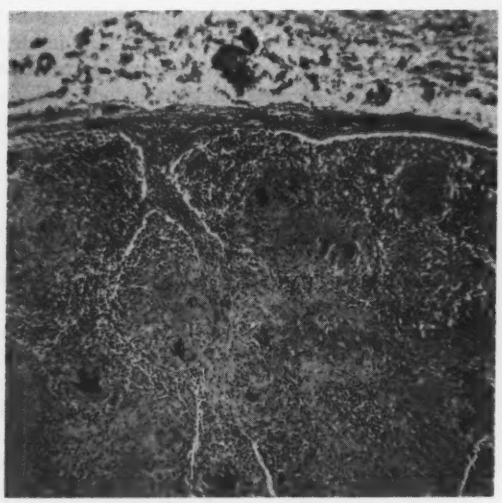


Figure 3. Lymph node containing multiple noncaseating granulomas. H and E. Green filter. ×63.

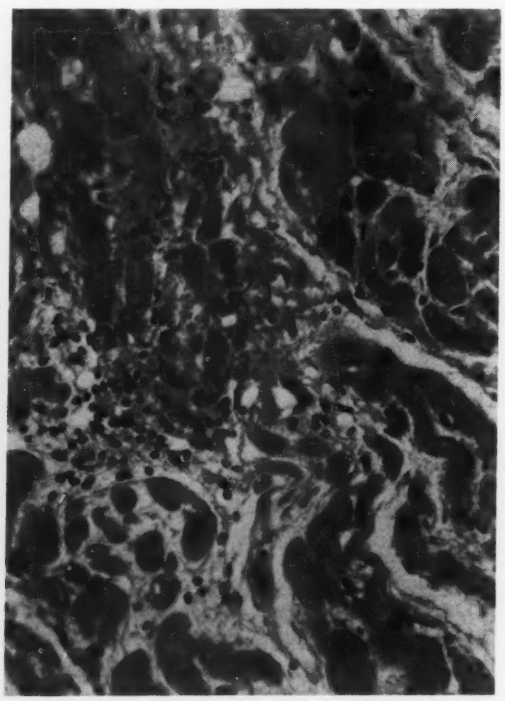


Figure 4. A focus of granulomatous inflammation in the myocardium. H and E. Green filter. ×290.

and to the pericardium and atria. Sometimes constrictive pericarditis and extensive cardiac involvement are present in sarcoidosis. In this case the cardiac involvement was so slight that little significance can be attributed to it.

The diagnosis of sarcoidosis is one of exclusion; it should not be made until the necessary historical, clinical, cultural and morphologic investigations have failed to identify a specific etiologic agent. This lesion was not recognized in time for all of these studies to be performed, but is compatible with sarcoid.

In review and in retrospect, the patient had multiple factors contributing to pulmonary hypertension and right heart failure; moderate mitral stenosis of long standing, the sarcoid-like granulomatous process and, terminally, pulmonary emboli.

Dr. Delp: Thank you, Dr. Klionsky. It is my own opinion that the patient had rheumatic valvular heart disease. She died for essentially the same reason and at about the same time that most patients with chronic rheumatic valvular heart disease die. The usual clue to this is, of course, the presence of valvular heart sounds and murmurs which, in this case, were not heard. I cling to the explanation that the murmurs were not heard because of the patient's degree of peripheral and general vascular collapse. That fact should always be uppermost in our minds when we see a patient in such a condition. Murmurs could be there under other circumstances, and rheumatic heart disease is a common type of heart disease. Although the sarcoidosis is an interesting finding, I do not attach much significance to it.

Pathological Anatomical Diagnosis

HEALED RHEUMATIC VALVULITIS OF THE MITRAL VALVE, with mitral stenosis, moderate and mitral insufficiency, slight.

FIBROCASEOUS GRANULOMAS of the upper lobe of the left lung and of the hilar lymph nodes, multiple (compatible with SARCOIDOSIS).

Granulomatous myocarditis, focal, slight.

Hypertrophy and dilatation of the left atrium, moderate; of the right ventricle, slight; dilatation of the right side of the heart, moderate.

Mural thrombosis of the left auricular appendage, advanced; of the right auricular appendage, slight.

Thrombosis of the left iliac and left ovarian veins, advanced.

RECENT INFARCTIONS OF THE LOWER LOBE OF THE RIGHT LUNG, multiple, advanced.

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Iodide Goiter

(Continued from page 479)

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Phenylketonuria—An Inborn Error of Metabolism

DAVID A. BALL, M.D., ***Kansas City, Missouri***

Phenylketonuria is but one of an ever growing list of diseases which is being defined in terms of some inherited defect. These diseases may seem to be unimportant from the standpoint of frequency of occurrence, however, their importance in terms of the knowledge they have provided about the nature of the body's metabolic processes and their dependence on hereditary control is of much greater importance. These inborn errors of metabolism have provided a common meeting ground for the fields of genetics, biochemistry, and clinical medicine and resulting from this meeting each of these fields has been strengthened.

OVER THE COURSE of several centuries physicians have gradually gained more complete understanding of numerous disease states. These advances have come only as the etiological factors in disease were understood. As medicine emerged from the realm of magic, rational theories of etiology were sought. At first the causes of disease were explained in terms of gross, morphological changes in the body and its organs. With the advent of the microscope, disease was studied at the level of the cell. In our own century the techniques of biochemistry and genetics have made it possible for physicians to trace the etiology of a certain number of diseases to the basic level of biological inheritance, the gene.

An increasing number of diseases are now understood to be related to the transmission of abnormal genetic material. These genetic diseases are assuming greater significance in clinical medicine as other categories of diseases such as nutritional and infectious diseases are brought under control. A group of the genetically produced diseases are expressed as disorders in metabolism and have thus been termed, "Inborn Errors of Metabolism." In this paper the conceptual basis of the inborn errors of metabolism will be discussed and this discussion illustrated with a specific disease, phenylketonuria.

It is a common observation that there is, within certain limits, rather wide individual variation of appearance and constitution within the human race. Part of this individuality in appearance and constitution results from man's great genetic diversity. In the human race genetically homogenous strains do not exist. With the exception of monovular twins, each person has a unique genetic inheritance. Man's individuality is a result of the blending of hereditary and environmental factors each of which has its own zone of influence. Environmental factors of extreme variety influence the expression of each person's individuality. However, this individuality within the environment is held within certain limits by hereditary or genetic factors. One example, pertinent to this discussion, of the limits established by genetic control, is the relative constancy of the body's chemical composition, and the uniformity in rate and direction of metabolic processes.

Occasionally, deviations from the normal limits occur in the chemical or metabolic constancy of the

This is one of a group of theses written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be best by the faculty at the school. David A. Ball, M.D., is now serving internship at St. Luke's Hospital, Kansas City, Missouri.

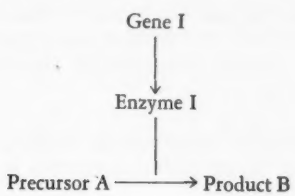
body. Some of these deviations produce so little effect that they go unnoticed. At other times these deviations produce effects of such magnitude that they may be properly termed a disease. Many of these deviations represent extremes of distribution of a trait, while others are the consequence of acquired dysfunction, such as the respiratory acidosis seen in advanced pulmonary emphysema. However, a rather significant number of these deviations represent inheritable disorders which can be directly attributed to a mutant gene. The inborn errors of metabolism are genetic produced deviations of sufficient magnitude to result in a disease state.

Inborn Errors of Metabolism

In 1908 Sir Archibold Garrod introduced the term "Inborn Errors of Metabolism." This concept was the result of his studies and observations on alkaptonuria, cystinuria, albinism, and pentosuria. Garrod proposed the concept that certain diseases of lifelong duration occurred as a result of blocks in the normal pathways of metabolism. He further postulated that these metabolic blocks were a result of the deficiency or inactivity of an enzyme. Forty years later Garrod's concept was extended to the genic level with the demonstration that each enzyme is dependent on the integrity of a specific gene.

In view of our present knowledge we may define an inborn metabolic error as a permanent, inherited condition due to a primary enzyme abnormality. Resulting from this enzyme abnormality one or more chemical compounds may follow an altered metabolic pathway and may produce either abnormally high or low concentrations of certain compounds in the body fluids. Such is the condition in phenylketonuria where the concentration of phenylalanine in the blood and cerebro-spinal fluid rises to abnormally high concentrations.

There is a common principle of etiological formulation which is relevant to all the inborn errors of metabolism. The mutant genetic information results in the enzymes related to the abnormal gene being formed with structural defects. The enzymes are proteins whose chemical activity is closely correlated to their structure. As the occurrence of each metabolic step is dependent upon a specific enzyme the alteration of any enzyme will be manifest as a failure in the metabolic step normally controlled by this enzyme. This may be illustrated as follows:



If Gene I is altered by a mutational event, Enzyme I will as a result be altered. Then Precursor A will not be converted to Product B at the normal rate. The genetic loss of capacity to create a normal enzyme results in disease if Precursor A has toxic effects or if Product B is required in some important biochemical reaction.

Phenylketonuria is an example of a disease produced by the accumulation of a toxic compound. Failure of the enzyme phenylalanine hydroxylase to convert phenylalanine to tyrosine results in the accumulation of abnormal quantities of phenylalanine. There are several examples of the situation in which the disease is the result of the failure to produce a necessary compound. Most mammals have an enzyme which will mediate a reaction for the formation of ascorbic acid. However in the entire human race the capacity for the endogenous formation of Vitamin C has been lost through the inheritance of a mutant gene. Thus man's diet must supply his needs for Vitamin C directly, or he will develop scurvy. Another way of stating this is that all human beings are afflicted with scurvy which is held in remission for most of us by the ascorbic acid supplied in our diet. Eventually the role of each of the amino acids and vitamins known to be essential in the human diet may be analyzed in terms of a single enzyme defect.

The term "molecular diseases" has been used to describe the inborn errors of metabolism. Pauling introduced this term in 1949 in connection with his studies of the inherited condition, sickle cell anemia. All of these diseases result from molecular defects in genes and subsequently in their related enzymes. It would appear likely that with further study the etiology of many more diseases both inherited and acquired will be traced to a molecular basis.

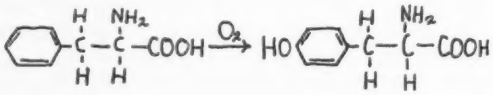
Now a word about the eugenic implications of the inborn metabolic errors. The majority of these diseases, including phenylketonuria, are transmitted as autosomal recessive traits. Recessivity reduces the dependence of the character on the gene. If the recessive gene is very rare the possibility of an individual receiving the mutant gene from each parent is very remote. Thus these offending genes are maintained in the population almost entirely by transmission through normal heterozygotes or carriers. These people carry the mutant gene, but because it is recessive it does not become manifest. Many diseases due to recessive genes have been identified in man, and undoubtedly many more will be identified. It is estimated that two people out of three are carriers of at least one serious recessive defect. As will be shown in the case of phenylketonuria, in all of these diseases consanguineous marriage greatly increases the probability of some undesirable recessive trait in the offspring. Due to the recessive nature of these diseases, the field of eugenics has little to offer toward their prevention at the present time. If methods were developed to more

accurately identify the heterozygotes for a wide variety of disease states then there would be definite eugenic application. At present the chief importance of the eugenic view-point is in advising parents of a child with an inherited disease as to the possibility of any further children being affected by the disease.

Phenylketonuria

In the remaining portion of this paper a specific inborn metabolic error, phenylketonuria will be discussed. The principles of etiological mechanisms as discussed in the preceding paragraphs are applicable to this disease.

Phenylketonuria is an inborn error of metabolism observed in mentally deficient patients and is characterized by the presence of phenylpyruvic acid in the urine. This disease was first described in 1934 by Folling, a Norwegian biochemist, who reported the presence of phenylpyruvic acid in the urine of ten mentally defective patients. In 1947 Jervis identified the basic metabolic abnormality in this disease as the inability to oxidize phenylalanine to tyrosine.



Phenylalanine is one of the amino acids which must be supplied by the diet. The minumum daily requirement of phenylalanine for an adult is about 1.10 grm. The normal metabolic pathway for the utilization of phenylalanine involves its conversion to tyrosine. The reverse of this reaction apparently does not occur to any significant degree. At least four of the body's hormones namely, epinephrine, norepinephrine, triiodothyronine and thyroxine, arise in metabolism from phenylalanine and tyrosine.

The normal level of phenylalanine in the serum ranges from 1 to 4 mgm. per 100 ml.; however, in phenylketonuria the serum levels of phenylalanine may range as high as 20 to 60 mgm. per 100 ml. Studies with isotopically labeled phenylalanine reveal that the rate of its conversion to tyrosine in children with phenylketonuria is only about one-tenth that of a normal individual. Thus with the failure of the normal metabolic pathways to deal with the phenylalanine provided in the diet, the phenylalanine level in the serum becomes quite high and results in secondary chemical abnormalities.

In 1939 Jervis demonstrated that phenylketonuria is a recessive condition transmitted by a single autosomal gene. It is present in each sex with equal frequency, since the gene is not located on the sex chromosomes. It has been clearly shown that the main features of this disease are the result of a single gene and not the composite result of several genes. The disease is present only in those individuals who receive two of the abnormal genes, one from each parent. The typical pattern of inheritance is from two apparently normal parents who are heterozygous for the disease. Following the Mendelian laws of inheritance, on the average one in four of their children will have phenylketonuria (homozygote), one will be normal and two apparently normal (heterozygotes). When a rare hereditary disease like phenylketonuria appears in a family there is frequently no antecedent case in the family history. This is due to the recessive nature of the abnormal gene which may be transmitted through heterozygotes for numerous generations. Thus the lack of previous cases in the family history is of no value in excluding inheritance as a factor in a rare recessive disorder.

In the United States the incidence of phenylketonuria is about 1 in every 40,000 of the population. Phenylketonurics constitute about 1 per cent of the institutionalized mental defectives. The calculated frequency of heterozygotes in the population is about 1 per cent. Thus the chance of a case of phenylketonuria occurring in a nonsanguineous marriage is 1/100 x 1/100 or 1 in 10,000. However in first cousin marriages the chance is increased to 1 in 800. Study of the families of phenylketonurics shows consanguinity to be present to some degree between about 8 per cent of the parents which is considerably higher than the 1 per cent incidence of consanguineous marriages in the general population. In general, the more rare the metabolic disease, the higher will be the incidence of consanguineous marriages among the parents of those affected with the disease.

The variety of clinical features seen in phenylketonurics have been carefully studied in a large number of patients. In keeping with the thesis presented in the introduction to this paper all the abnormalities seen in phenylketonuria should be viewed as either near or remote results of the failure in oxidation of phenylalanine to tyrosine.

The majority of phenylketonurics are idiots. About one half of these patients never learn to talk and about one third are unable to learn to walk. A small group of phenylketonurics may be classed as borderline mental defectives, but seldom is their I.Q. above 80. The degree of mental retardation is usually stable as progressive mental deterioration is seldom part of the disease picture.

There are no neuropathological findings regularly present in this disease to explain the clinical picture; however, localized or diffuse demyelination has been found in a certain percentage of individuals with phenylketonuria.

The neurological findings in phenylketonuria include hyperactive deep tendon reflexes, muscular hypertonicity, ataxia and tremors. The behavior of

phenylketonurics is described as restless, jerky, fearful, hyperactive and irritable. They frequently exhibit a repetitive, manneristic type of behavior. About one-fourth of the phenylketonuric patients have a history of convulsive seizures. The electroencephalographic findings in these patients are abnormal, however they are not diagnostic.

Phenylketonurics are generally of light complexion and typically have blond hair and blue eyes. They are often described as attractive children in contrast to the usual appearance of the mentally defective child. It has been shown that there is a measurable defect in the amount of skin pigmentation of phenylketonurics. The mechanism of this defect is not known, but it probably involves an alteration in the metabolism of tyrosine which is the normal precursor of melanin. The coloration of phenylketonurics is generally lighter than that of the parents. The hair and skin tend to become darker when the patient is maintained on a low phenylalanine diet.

In phenylketonuria the primary or central biochemical defect is the failure of the oxidation of phenylalanine to tyrosine. The chemical findings which confirms this are the excessively high blood levels of phenylalanine, the absence of a rise in blood tyrosine after the ingestion of phenylalanine and the very restricted conversion of labeled phenylalanine to tyrosine. The inactive enzyme in these patients has been identified as phenylalanine hydroxylase which is normally present in the liver.

The excessively high level of phenylalanine in the blood and spinal fluid results in several abnormal conditions. First the excessive phenylalanine is partially converted by its transaminase to phenylpyruvic acid which in turn is converted to phenyllactic acid, phenylacetic acid, and phenylacetylglutamine all of which are excreted in the urine. Second the excess of phenylalanine inhibits normal pathways of tyrosine metabolism with a resulting partial defect in skin pigmentation. Third the high levels of phenylalanine or one of its products causes some, as yet unexplained, damage to the central nervous system resulting in mental retardation, seizures, and the other neurological abnormalities.

Individuals who are heterozygous for phenylketonuria have no clinical manifestations of the disease. However it is possible to identify the heterozygotes by means of a phenylalanine tolerance test. Parents of phenylketonurics when given a specific dose of phenylalanine show a higher and more sustained concentration of phenylalanine than do controls. These results suggest that the heterozygous carriers with one defective gene have less than the normal complement of active phenylalanine hydroxylase.

The diagnosis of phenylketonuria should be ruled out in all cases of mental retardation. The diagnosis is made by demonstrating the presence of phenylpyruvic acid in the urine. When a few drops of 10 per cent ferric chloride solution are added to an acidified urine specimen an intense green color develops if phenylpyruvic acid is present. A urine moist diaper may be tested easily by the same method if a urine specimen is not available. In addition a paper reagent strip (Phenistix) is available which is specific for the detection of phenylketonuria. Thus the laboratory diagnosis of phenylketonuria is quite simple. It is important that the diagnosis be made while the patient is very young due to the prospects of considerable gain from the institution of treatment early in life.

Several studies have been made on patients with phenylketonuria with regards to the effect of diet on the disease process. In these studies phenylketonurics of all ages have been maintained for several months on diets which have a very low content of phenylalanine. Beneficial effects on intelligence were limited to patients under three years of age. Improvements in general behavior, EEG's, and skin condition were observed in some older patients. However, the problems involved in maintaining a low phenylalanine diet which is nutritionally adequate are considerable. The basis of the special diet used in the management of phenylketonuria is a synthetic mixture of essential amino acids which is made by hydrolyzing the milk protein, casein and removing the phenylalanine. It is not possible to devise a home diet which is sufficiently free of phenylalanine and yet adequate in the protein required for growth and maintenance.

The observations made during the course of these dietary studies indicates that the metabolic disturbances associated with the high concentrations of phenylalanine in the plasma interfere with normal cerebral development rather than with the function of a normally developed brain. Thus any effort to alleviate the effects of this disease must be instituted early in life to prevent irreversible damage to the central nervous system.

At the present time only a small number of children with phenylketonuria have been treated with a low phenylalanine diet since early infancy, however it is encouraging that all of the children in these studies appear to be developing normally. It has not been determined how long it will be necessary for phenylketonurics to be maintained on a special diet, however some observations suggest that the diet may not be necessary beyond two or three years of age. It is possible that some time in the future the missing enzyme may be isolated in a suitable preparation to administer to these patients so that a special diet would not be necessary.

Editor's Note: References may be obtained by writing The JOURNAL, 315 West Fourth Street, Topeka, Kansas.

From the Stacks

State Medical Library

MRS. BLENDENA EVANS, *Librarian*
Stormont Medical Library, State House
Room 516, Topeka, Kansas
Telephone: Central 5-0011, ex. 297 or 298

Monographs Available in This Library

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(Continued on page 500)

The President's Message

DEAR DOCTOR:

This being my first President's Page, I feel I am not in an enviable position, though greatly honored to have been asked to fill the vacancy of our distinguished president, now deceased; a great man of medicine, a quiet, sincere, religious gentleman with the great respect of all.

Following is a short report regarding our trip to St. Louis attending the one-day conference of the United States Chamber of Commerce. It was attended only by the higher echelon of business with invitations to presidents and executive secretaries of medical societies. The entire program was pointed as to what could be done to forestall the socialistic trends of the Federal government in business, medicine, and allied interests. They suggested training programs in economics and participation in politics on the local level.

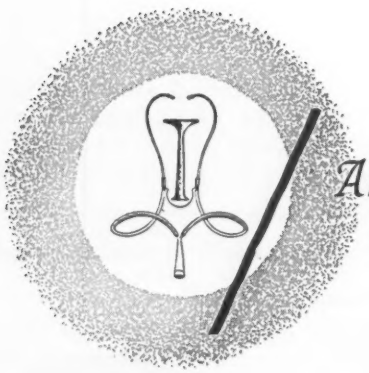
From the information obtained, I feel that medicine could only participate from the local level by contact education, very similar to the suggestions of the American Medical Association.

I hope the medical profession will take more interest in public relations and to further educate the public in our side of the story regarding Federal medical legislation.

In attending and acting as moderator at the postgraduate course in School Health, October 19, 1961, one could not help but be impressed with the tremendous job the Kansas University Medical School is doing in the field of postgraduate study. It has been growing each year until it has reached the stature of being one of the best in the United States and certainly deserves the attention and participation of the doctors throughout the state.

Yours very truly,

President



Announcements

Professional meetings, conferences, and postgraduate courses of national importance are listed for the* DOCTOR'S CALENDAR. *Notice of the session is posted in advance to allow the physician time to make preparations.

There are still approximately twenty-five seats which have not been reserved by the $100 deposit necessary for the Charter Flight to Europe in June, 1962. It is necessary that the airship be contracted for within the next month. Anyone interested please contact Dr. John Shellito or Dr. John Warren, 3244 East Douglas, Wichita, Kansas.

MEDICO is increasing the number of medical personnel serving in its overseas hospital and clinic installations. There are fifteen MEDICO-supported units in twelve countries in various parts of the world. New requests are being received for additional medical and surgical teams in South America and in the newly emerging countries in Africa.

At present, surgeons, internists, general practitioners, and anaesthesia specialists are needed in Afghanistan, Cambodia, Vietnam, Malaya, Laos, and Haiti. Salaries, length of service and specific information concerning each project will be sent on request. Address inquiries to MEDICO Incorporated, 420 Lexington Avenue, New York 17, New York.

The Department of Medicine of the Menorah Medical Center will hold its annual A. Morris Ginsberg Memorial Seminar on November 28 and 29, 1961. The guest this year will be Joseph B. Kirsner, Ph.D., M.D., Professor of Medicine, University of Chicago.

All physicians are invited to attend. The general subject will concern Diagnosis and Management of Gastrointestinal disorders.

The Third National Conference on the Medical Aspects of Sports sponsored by the American Medical Association, under the auspices of the AMA Committee on the Medical Aspects of Sports, will be held in Denver, Colorado, at the Cosmopolitan Hotel on November 26, 1961. The Conference will be held in conjunction with the annual Clinical Meeting of the American Medical Association, November 26-30, 1961.

Those interested in receiving announcements concerning the Conference should address the Secretary, Committee on the Medical Aspects of Sports, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

The Association of the American Medical Col- leges today announced the extension of the Foreign Fellowships for Medical Students program which is sponsored by Smith Kline & French Laboratories, Philadelphia pharmaceutical firm.

Originally set up for a 3-year term and due to expire in 1962, the program is to be extended through 1963.

NEW MEMBERS

The JOURNAL *takes this opportunity to welcome these new members into the Kansas Medical Society.*

Keith W. Gallehugh, M.D.
1400 Polk
Great Bend, Kansas

Gordon E. Maxwell, M.D.
135 E. Claflin
Salina, Kansas

George E. Miller, Jr., M.D.
135 E. Claflin
Salina, Kansas

William A. Smiley, Jr., M.D.
1011 Center Avenue
Goodland, Kansas

John G. Swails, M.D.
Wathena, Kansas

Blue Shield

Supplemental Benefits

(Editor's Note: In the October issue of the JOURNAL OF THE KANSAS MEDICAL SOCIETY, *we carried a discussion of the second annual enrollment of federal workers under the Federal Employee Health Benefits Legislation. There is sufficient interest in the Blue Shield benefits under this program, that it seems appropriate to discuss the Blue Cross-Blue Shield Supplemental Benefits this month inasmuch as only the basic benefits were discussed in October.)*

The Deductible

The "deductible" is the amount of expense a subscriber must incur for covered services or supplies *before* the Plan will pay Supplemental Benefits. The Deductible is $100 under the High Option program and $150 under the Low Option program. Expenses paid for by Basic Benefits are not counted toward the Deductible; nor will Supplemental Benefits reimburse the subscriber for the Deductible.

A separate Deductible applies for each subscriber during a Benefit Period and all members of the Federal Employees Plan administered by Blue Cross-Blue Shield are eligible for Supplemental Benefits. If two or more subscribers under the same family enrollment are injured in the same accident, *only one* Deductible need be satisfied by those injured, however.

The Benefit Period

A Benefit Period begins on the first day that a charge for covered services or supplies is incurred after the subscriber's coverage under this Plan first becomes effective; or on the first day that such a charge is incurred after the termination of a previous Benefit Period. In either case, the Benefit Period begins with the first incurred charge for covered services or supplies even though such charge is covered by Basic Benefits. An expense is "incurred" on the date the service or supply for which a charge is made is received. A Benefit Period ends twelve months after it begins.

What Is a Covered Service?

- Physicians' services, including surgery, home, office and hospital visits and consultations.
- Hospital services; however, any part of the hospital's charge for room and board in excess of $25 a day (High Option) or $15 a day (Low Option) will not be allowed as a charge for a covered service.
- Anesthetics and administration.
- Oxygen and equipment for administration.
- Blood transfusions, including the cost of blood, blood plasma and blood plasma expanders.
- Radiation therapy.
- Diagnostic examinations, including x-ray, laboratory, basal metabolism, electrocardiogram, electroencephalograms and radioisotope.
- Local professional ambulance service to or from a hospital for inpatients, or for outpatients receiving accident care.
- Physical therapy rendered by a qualified professional physical therapist.
- Orthopedic braces (except corrective shoes), crutches, and prosthetic appliances such as artificial limbs and eyes, including their replacement, repair or adjustment.
- Rental of wheelchair and other durable equipment for medical treatment.
- Drugs and medicines requiring a written prescription.
- Services of special nurses in or out of the hospital; or a licensed practical nurse in the hospital.

However, under unusual circumstances, and upon written certificaton by the attending physician that the services of a professional registered nurse were necessary but unobtainable, the Carrier may determine that the services of a licensed practical nurse are covered services.

Amount of Payment

The Plan will pay Supplemental Benefits of 80 per cent under the High Option or 75 per cent under the Low Option of charges for covered services and supplies which are in excess of the $100 (High Option) or $150 (Low Option) Deductible. However, in the case of nervous or mental disorders, under both options the Plan will pay 50 per cent of charges in excess of the applicable Deductible for covered services and supplies (including drugs and medicines) received in the outpatient department of a hospital or outside of a hospital.

Submitting a Claim

As it was pointed out last month, Service Statements for basic benefits are submitted by the physician on the regular Blue Shield form.

To submit for Supplemental Benefits, *the subscriber* must file a *special* claim after the Deductible has been satisfied. The subscriber should have forms in a kit which was distributed or the forms can be obtained from his personnel office, or by writing to the Blue Cross-Blue Shield office, in Topeka. The number, on this form, is FSP-1361. This completed form, plus the itemized bills for the medical expense should be sent to Kansas Blue Shield, Topeka. The only people who do not submit claims to Topeka, are those enrolled in Johnson and Wyandotte Counties, and these will be submitted to Blue Cross-Blue Shield, Kansas City, Missouri.

Supplemental Benefits are paid to the subscriber except in very unusual circumstances where an assignment has been obtained from the Federal Employee. More information on these special assignments is available from the Physician Relations Department of Kansas Blue Shield, Topeka.

Special Benefit Provisions

To the extent that they are not covered by Basic Benefits, a certain amount (depending on the high or low option program in which the member is enrolled) will be paid toward the following services in a physician's office, or elsewhere:

- X-ray examinations.
- Laboratory examinations.
- Basal metabolism examinations.
- Electrocardiograms.
- Electroencephalograms.
- Radioisotope examinations.

These benefits are paid regardless of whether the subscriber has satisfied the Deductible. The $20 (High Option) or $25 (Low Option) payable by the subscriber may be used to help satisfy the Deductible the member may have. If the Deductible has already been satisfied at the time the subscriber receives a service for which the special benefit is payable, Supplemental Benefits will be paid for the charges including high or low option.

There Are Exclusions!

It should be pointed out here that basic, maternity or supplemental benefits will *not* be provided for charges incurred for any of the following:

Services and supplies—

- Furnished without charge, or paid for by a government.
- For which the subscriber has no legal obligation to pay, or for which no charge would be made if the subscriber had no health insurance coverage.
- Required as a result of war, or act of war, occurring after the effective date of the subscriber's coverage.
- Required as a result of occupational disease or injury for which any benefit is payable under workmen's compensation or similar law.
- For personal comfort, such as radio and telephone, beauty or barber services.
- For cosmetic purposes unless related to an accidental injury occurring while the subscriber is covered under this Plan; however, Basic Hospital Benefits are provided even if the hospital admission is for cosmetic purposes not related to accidental injury.
- For routine or periodic physical examinations, screening examinations, immunization shots, the removal of corns or calluses or the trimming of toenails.
- Not medically necessary for the diagnosis or treatment of an illness, injury or bodily malfunction.

Convalescent, custodial or rest cure care is not covered; travel, even though prescribed by a physician is not covered; eyeglasses or hearing aids or examinations for them; physicians' visits for the routine care or examination of a newborn child.

SUPPLEMENTAL BENEFITS will not be provided for:

A. Dental care, dental surgery, or dental appliances unless required by accidental bodily injury occurring while the subscriber is covered under this Plan; except covered oral surgery is not excluded.

B. Services or supplies required for obstetrical delivery other than caesarean delivery or the complications of pregnancy.

C. Services or supplies to the extent benefits are available to the subscriber under any other health benefits plan held by reason of law or as a result of

(Continued on page 500)

Personalities—IN KANSAS MEDICINE

Dr. Arthur C. Cherry, Jr., of the Topeka Medical Center has been elected a Fellow of the American Academy of Pediatrics.

Dr. Hugh Bayles has been elected chief of staff of the St. Margaret's Mercy Hospital in Fredonia.

Dr. Edmer Beebe, Olathe, and **Dr. Richard E. Speirs,** Dodge City, have been appointed by Gov. John Anderson to the state board of healing arts.

Dr. Robert Stoffer and **Dr. Emmett McCusker** of the Hertzler Clinic, Halstead, attended the sessions of the American Association of Medical Clinics in New York.

Dr. Frances Allen, Newton, was the delegate from Bethel Clinic to the meeting of the American Association of Medical Clinics which was held in New York the latter part of September.

Great Bend pediatrician, **Dr. Marion Russell,** has a role in two University of Kansas Extension Clinics being conducted in Western Kansas this fall.

Dr. David W. Robinson, a Johnson County surgeon is on his way to Vellore, India to give of his time and knowledge to the teaching of medical students in his field of plastic surgery.

Dr. Norman E. Macy of Wichita, formerly of Longford, has been awarded a four-year followship to study general surgery at the Mayo Brothers Clinic at Rochester, Minn.

Dr. L. E. Haughey of the Gelvin-Haughey Clinic, Concordia, attended a meeting of the American Association of Medical Clinics in New York.

Drs. Robert W. Webber and **James C. Dowell** have started practices of internal medicine in Salina. Their offices are at 416 S. Santa Fe.

Dr. James J. Jambor, Dodge City physician, spoke and showed slides on dermatology at the Lions Club. Dr. Jambor spoke on common ailments and ways of treating them.

Kansans were among the 1,100 surgeons inducted as fellows of the American College of Surgeons. They were **Dr. Clarence H. Steele,** Kansas City; **Dr. Charles A. Isaac,** Newton; and **Dr. Kenneth D. Powers,** Wichita.

Dr. H. O. Marsh, Wichita, has been selected as chairman of the Medical Advisory Committee of the Sedgwick County Chapter of the National Foundation.

Dr. Gaylord P. Neighbor or Kansas City was elected president of the Kansas Academy of General Practitioners at the close of the 11th annual convention in Wichita.

Other officers are: **Dr. Norman H. Overholzer,** El Dorado, president-elect; **Dr. Floyd Beelman,** Topeka, vice-president; and **Dr. Galen Fields,** Scott City, secretary.

Drs. Thomas P. Butcher and **J. L. Morgan,** Emporia, took part in the program for the annual meeting of the Kansas Tuberculosis and Health

(Continued on page 500)

The Kansas Press Looks at Medicine

Editor's Note. In this section the* JOURNAL *reproduces editorials relating to medicine which have appeared in the lay press. An effort is made to include both favorable and unfavorable comments, and the Editorial Board in no instance assumes responsibility for the opinions expressed.

HEALTH COST TEST

All plans to attack the health insurance problem are interesting, including the one being developed by the California Medical Association.

The voluntary program there, which is expected to be in full operation after two years, would cost $24 per month and would cover 90 per cent of the health-care costs of the average family.

Realizing that 72 per cent of all Californians are now covered by private health insurance plans, the doctors are working on the "segmented" approach. It would supplement existing programs to the point where a family of four would have 90 per cent coverage for hospitalization, medical services, health check-ups, laboratory fees and some psychiatric care. It is expected the plan would continue to cover people after they reach 65.

If this program can be applied nationally, the sponsors expect it will end public pressure for government-financed health care. The test will be how many families will want to budget $24 per month for this protection.—*Wichita Evening Eagle & Beacon,* September 5, 1961.

UNCLE SAM, M.D.

Uncle Sam is going into the health business in a big way if President Kennedy can sell Congress on his six-point proposal for Federal intervention in the fields of medical services and education, hospitalization, medical research, vocational rehabilitation and "youth fitness."

The most controversial item is a revival (with some revisions) of the medical care for the aged program that was rejected by Congress last year. Under the new specifications, the estimated cost of $1.5 billion is to be met by a hike in Social Security taxes.

The five other programs to be paid for with increased outlays of tax money are loosely figured to cost something over $56 million for the first year and $170 million the second year and include construction of nursing homes and medical and dental schools, Federal medical and dental scholarships.

The President insisted in his message that "This is not a program of socialized medicine." It "guaranteed," he said, freedom of choice of doctor and hospital and is "in accordance with the traditional American system of placing responsibility on the employee and the employer rather than on the general taxpayer, to help finance retirement and health costs."

We had somehow felt the "traditional American system" involved looking out for oneself and one's kith and kin.

Nor is there any "freedom of choice" involved in payment of the increased Social Security taxes—even among those who are providing their own health insurance.

Nor can we conceive of the government barging into the healing business in any large way without regimenting the medical profession and entailing the customary extravagance, inefficiency and bureaucratic arrogance.

Such a proposal would be of little surprise in a socialistic government, but serious considerations of them in our democratic government are almost unbelievable.—*Pratt Daily Tribune,* February 14, 1961.

USE YOUR MEDICAL LIBRARIES

YOUR LIBRARIAN WILL BE HAPPY TO ASSIST YOU

Hearing Disorders

Loss of hearing, a condition that afflicts nearly 6,000,000 Americans, is the leading physical disability in this country, according to a recent issue of *Patterns of Disease,* a Parke, Davis & Company publication for the medical profession.

There are, the report estimates, 24,000,000 disabilities among persons in the United States, excluding those in institutions. Of these disabilities, 25 per cent are some degree of deafness, although only a relatively small number of persons—109,000—can be considered totally deaf. And deafness is more common among men than women, the rate per 1,000 persons being one third greater for males.

Contrary to common belief, being hard of hearing is not primarily an old folks' complaint. In fact, almost three out of every five persons with hearing disorders are under 65. But incidence of deafness does increase with age, and after 65, its rise is sharp. In the 45-64 age group, for instance, the number of persons with hearing impairments is 52 per 1,000 people, but for the 65-74 the rate is 129 per 1,000 persons. After 75, the rate soars to 256 per 1,000 population.

Numerous Causes

The causes of hearing disorders are as varied as they are numerous. Certain causes, however, are attracting increased attention either because of new knowledge about them or because they are becoming increasing problems.

For example, it has been found that complications of pregnancy and birth account for a high percentage of hearing disorders among newborn babies and young children. Findings of a study conducted among 328 children with severe hearing loss revealed that in one third of the group, damage could be attributed to the prenatal or natal periods. Complications of birth and labor headed the list of specific causes, accounting for more than 15 per cent of all cases. Maternal rubella was found to be the cause of 11 per cent of cases and Rh incompatibility was believed responsible for 7 per cent.

Noise is another cause of deafness that is attracting growing concern and interest. For, with the expansion of industry and the development of high-speed machines, noise-induced hearing loss is becoming an increasingly serious problem.

The incidence of hearing loss due to noise depends on such factors as the level of sound, frequency of noise in cycles per second, the duration of the noise and the susceptibility of the individual. For example, brief exposure to a loud noise, like that of a jet engine, may have no significant effect. But prolonged exposure to a lesser volume of noise, such as that of subways, may cause damage. And if noise is both prolonged and intense it will produce "permanent damage to the inner ear, varying from minor changes in the endings of hair cells to complete destruction of the organ of Corti."

However, noise may cause hearing loss without causing permanent damage. In many cases, the loss is only temporary. If a person is exposed to noise on the job, his hearing may be affected by the end of the work-day, but by next morning, his ears will probably have recovered and his hearing will be back to normal.

Noise has become an important factor in deafness, particularly among men. Almost one out of every five hearing impairments in men is caused by injury, which has been attributed to the higher accident rate for men and their exposure to noise in industry, as compared to only one in 25 among women.

Surgical Techniques

If hearing impairment is becoming an increasingly serious problem, it is also a field in which rapid advances are being made. Hearing aids are proving valuable in overcoming certain types of deafness, and new surgical techniques are also achieving a wide measure of success.

Particularly encouraging have been the results of surgery in treating otosclerosis, a condition responsible for about one in every five cases of impaired hearing. Another new operation, tympanoplasty, has proved "useful in restoring tympanic function when the conduction mechanisms involving the middle ear have been damaged by chronic middle-ear or mastoid diseases."

Symptoms Vary

The symptoms and signs of impaired hearing vary greatly, depending on the type of deafness the individual has. To a person with one type of deafness, the sound of his own voice may seem loud; to someone with another type, it may seem soft. Vertigo may be present in some types of deafness, in others it is rare.

People with tinnitus—ringing or buzzing in the ears—may not even be aware that they have impaired hearing. Results of a study conducted among persons complaining of tinnitus revealed that more than 92 per cent were found to have hearing losses when tested audiometrically. Curiously enough, however, only 53 per cent had been aware that their hearing was impaired.

Failure to recognize deafness is, of course, fairly common, particularly where children are concerned.

With the aid of special testing devices, the hearing of babies and young children can be accurately measured. Even infants only three weeks old can be tested for response to sound stimuli.

Hearing impairments should be detected as early as possible, for differential diagnosis in infants and young children is necessary to rule out such factors as mental retardation, aphasia, emotional disturbance, and psychic deafness.

From the Stacks

(Continued from page 492)

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Mitchell, H. H. Nutrition and climatic stress. Thomas. 1951.

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National Research Council. Survey of food and nutrition research in the U. S. 1948-1953.

Blue Shield

(Continued from page 496)

employment when the employer contributes toward the cost of the plan or makes payroll deductions for collections of premium.

D. Services of a special nurse who is an immediate relative, or member of the household of the subscriber. However, this exclusion does *not* apply to the services of such special nurse for one 8-hour shift out of each 24-hour continuous nursing period if satisfactory proof is furnished that she would otherwise be gainfully employed as a nurse.

Maximum Supplemental Benefits

The maximum Supplemental Benefits payable are *$10,000 for one benefit period or $30,000 for three or more benefit periods under the High Option program; or $5,000 for one benefit period and $10,000 for three or more benefit periods under the Low Option program.*

When these maximum amounts have been paid under either program, Supplemental Benefits can be reinstated upon submission of evidence, acceptable to the Carrier, of the subscriber's insurability. The Deductible and the above maximums apply *only* to Supplemental Benefits.

Personalities

(Continued from page 497)

Association and its medical branch, the Kansas Thoracic Society, in Topeka.

The 1961-62 officers of the Kansas Thoracic Society are: President, **Paul R. Carpenter, M.D.,** Kansas City; Secretary-Treasurer, **M. Martin Halley, M.D.,** Topeka. Representatives-at-large to Executive Committee: **I. S. Kwak, M.D.,** Norton, and **James C. Dowell, M.D.,** Salina. Representative Councilor to A.T.S. is **Martin J. FitzPatrick, M.D.,** Kansas City. They were elected at the annual meeting of the Kansas Thoracic Society in Topeka on September 28, 1961.

James Dowell, M.D., and **C. F. Haughey, M.D.,** Salina, appeared on the program of the Annual Meeting of the Kansas Tuberculosis and Health Association and the Kansas Thoracic Society in Topeka September 28 and 29.

Power Mower Kills Child

The power lawn mower recently took a life. The victim was a two-year-old Kansas girl, who ran in front of a riding-type lawn mower being operated by her father. He had made a turn and did not see his little girl in time. He was admitted to a hospital for treatment of a severed tendon and a cut knee, resulting from his frantic effort to brush his daughter out of danger. The lawn mower had no guard on the front.

The State Board of Health believes the power lawn mower accident rate has assumed epidemic proportions. If as many persons became ill with smallpox as are injured by power mowers every person in the nation would rush to have himself vaccinated against smallpox. And, of course, that's the only way to stop an epidemic—by doing something to prevent its further occurrence. Apparently not enough people are concerned about the power mower accident epidemic. This attitude is similar to the apathy toward car accidents.

Almost every issue of our newspapers carries an account of one or more injuries involving power mowers. Some injuries are relatively minor, some are serious but can be successfully treated, some permanently disable the victims, some are fatal. Most of them could be prevented.

Obituaries

HERBERT CILLIS MARTIN, M.D.

Dr. Herbert Martin, 45, a Coffeyville physician since 1946, died in Coffeyville Memorial Hospital on September 24, 1961. Death was attributed to cancer.

Dr. Martin was born in Coffeyville, December 11, 1915. He graduated from the University of Kansas Medical School in 1942. His internship was served at Grace Hospital in Detroit, Michigan. Upon completion of his internship, Dr. Martin entered the armed services, serving with the Army Medical Corps overseas.

Dr. Martin was a member of the First Methodist Church. He held memberships in the American Medical Association, the American Association of General Practitioners, the Masonic Lodge, and the Coffeyville Memorial Hospital medical staff.

Surviving in addition to his wife and mother are four children, Anita Sue, Scott, Stewart, and David, all of the home; and a brother, Dr. Albert E. Martin.

ERNEST M. SEYDELL, M.D.

Dr. E. M. Seydell, 79, Otolaryngologist and practitioner in Wichita since 1909, died September 23, 1961, in Wesley Hospital.

Dr. Seydell was born in Chicago, March 29, 1882 and was graduated from Northwestern University Medical School in 1909. He went to Wichita after graduation and served his internship in the pathology department at St. Francis Hospital.

He was a specialist certified by the American Board of Otolaryngology in 1925. He later became a member of the Board of Otolaryngology. He was associate editor of the *Archives of Otolaryngology* for many years; member of the American Academy of Ophthalmology and Otolaryngology and he held memberships to many other organizations.

He is survived by his wife, two daughters, one son, four grandchildren and one great-grandchild.

The Kansas Medical Society—1961-1962

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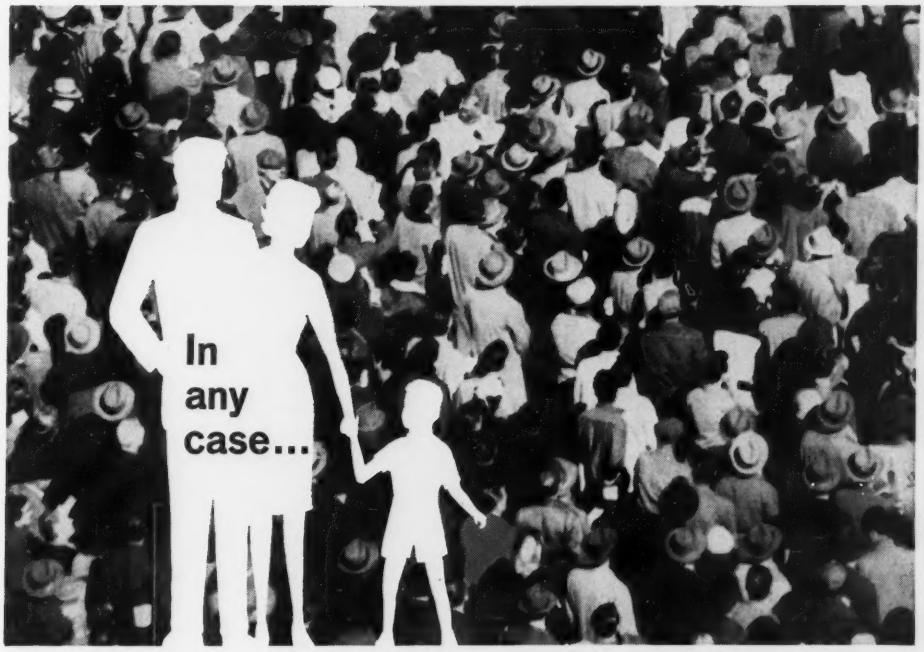

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*Journal of AMA, Vol. 169, No. 1, pp. 41/109

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1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases "Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2] 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis "It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . ."[3]
3. Fernandez-Herlihy, L: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.[4] Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.[5] 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases "Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult."[6] 6. Overholser, W., and Fong, T.C.C. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.[7] 7. Goldsmith, G A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec.10) 1960.

diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.[8] "Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes."[9]
8. Duncan G. G.: Diseases of Metabolism 4th edition W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

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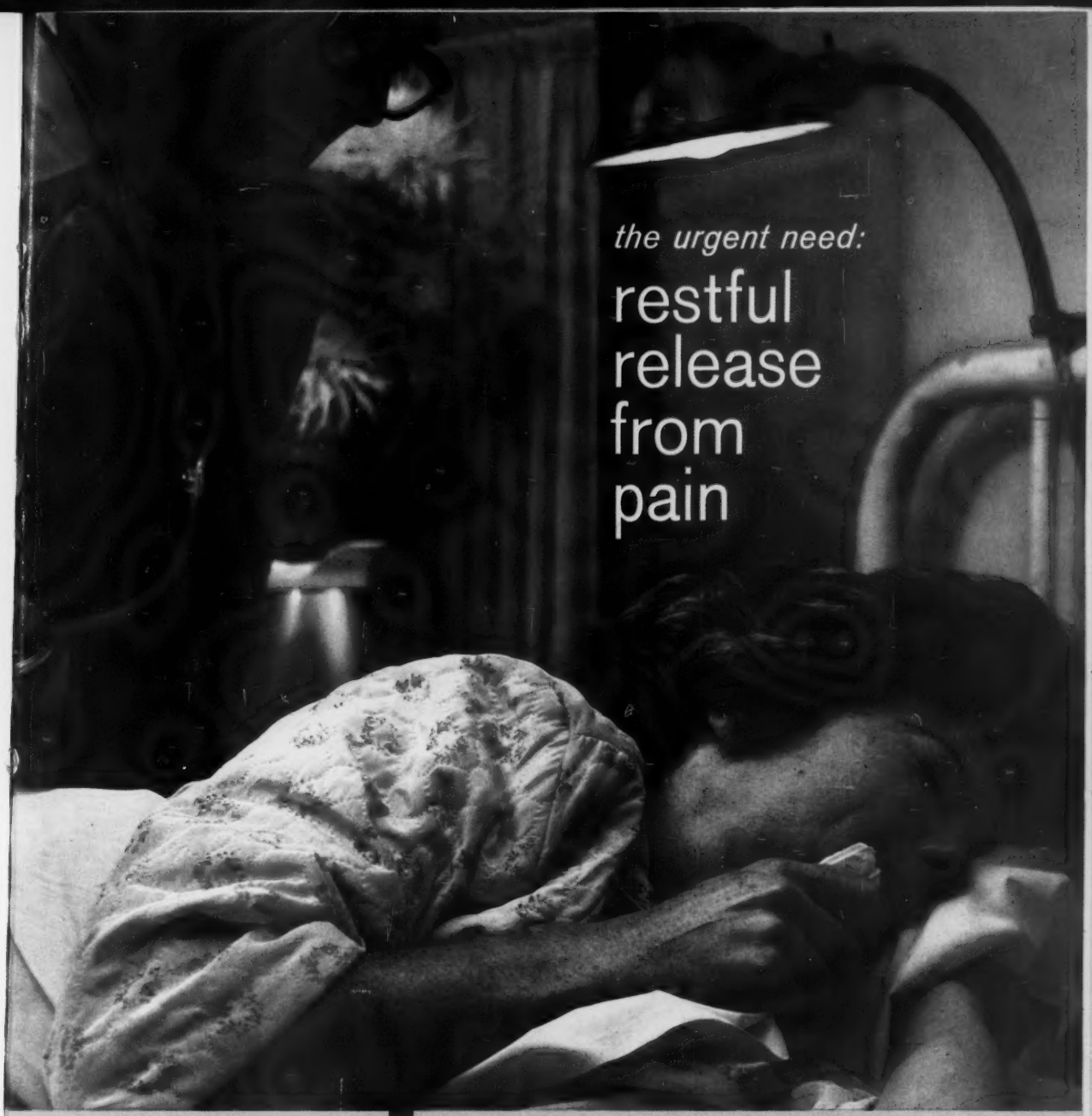

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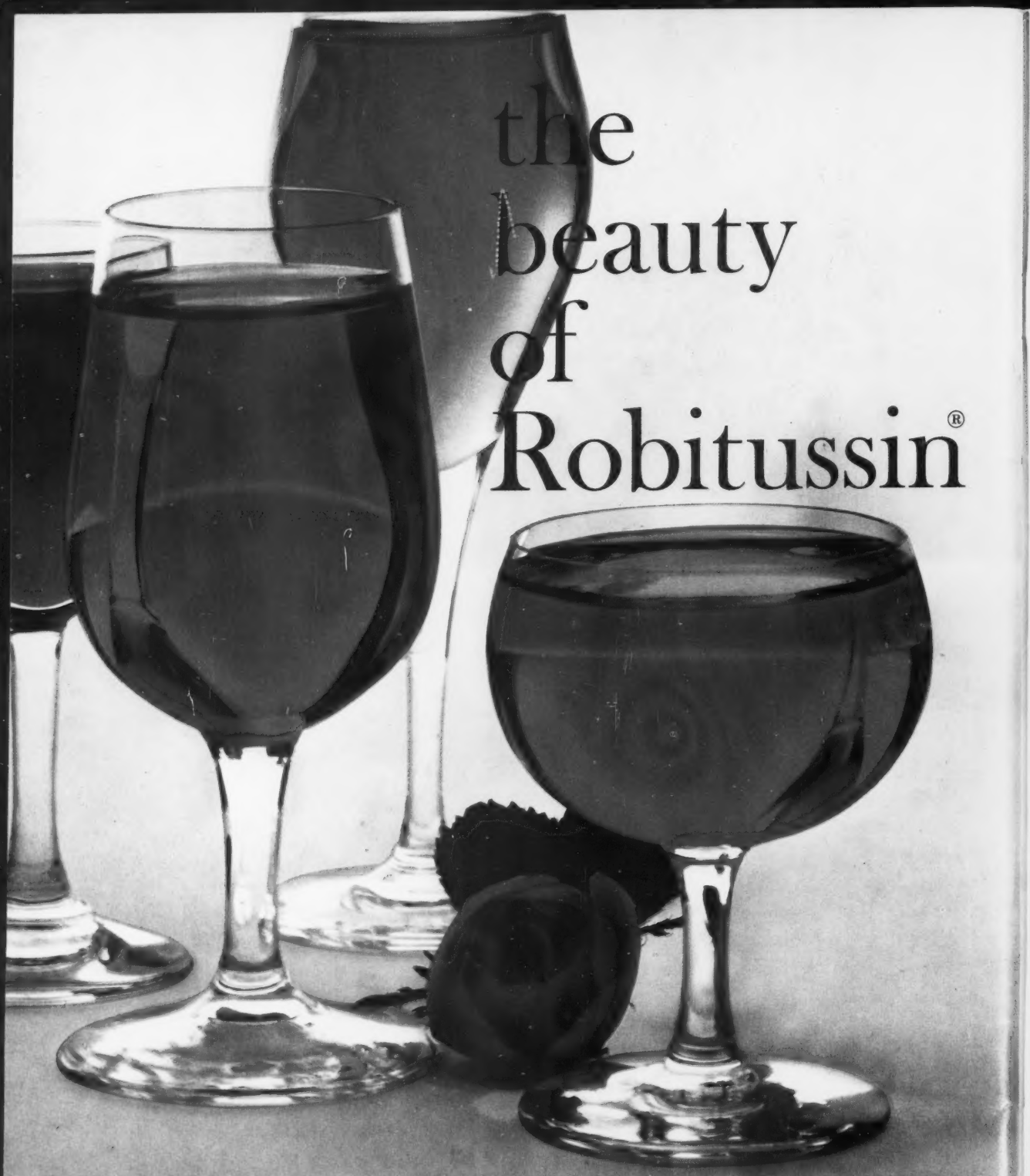

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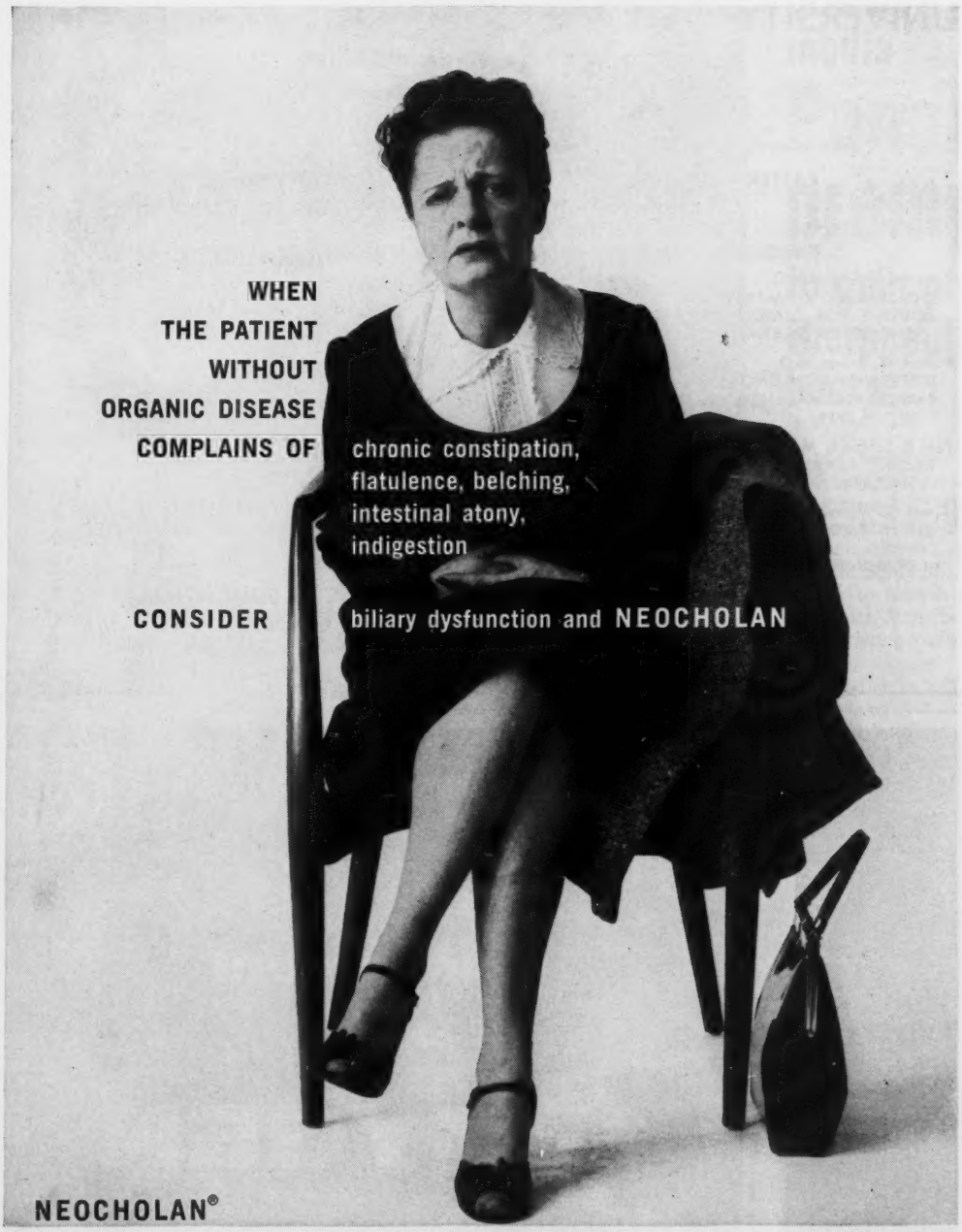

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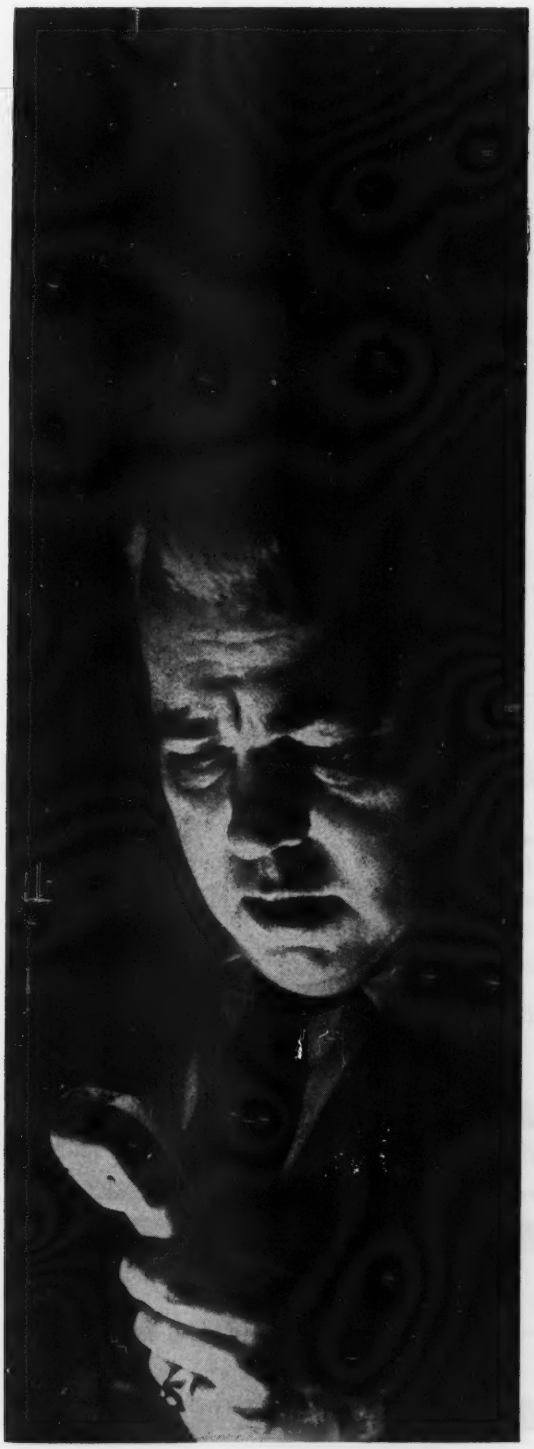

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(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., et al.: Diabetes 7:398, 1958.

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Bibliography: (1) Jacobs, I.: GP *21*:93 (Jan.) 1960. (2) Shulman, I.: J.A.M.A. *175*:118-123 (Jan 14) 1961. (3) Moore, C. V., in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1960, p. 243.

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